

Metabolic Syndrome, Abnormal Glucose Tolerance and High Sensitivity-C-Reactive Protein among Women with a History of Gestational Diabetes Mellitus

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Abstract

Background: Gestational Diabetes Mellitus (GDM) is a risk factor for diabetes and cardiovascular diseases. Early detection of cardio-metabolic risks is recommended for management. This study evaluated the associations between Metabolic Syndrome (MetS), abnormal glucose tolerance and cardiovascular risk factors in Malaysian women with prior GDM.

Method: Seventy-seven, non-diabetic women post-GDM, aged 20-40 years (mean BMI: 26.4 ± 4.6kg/m²) with high type 2 diabetes risks, were evaluated at a median of four months postpartum. Their anthropometric and biochemical measurements were obtained.

Results: The overall prevalence of MetS and dysglycaemia were 22% and 29% respectively. Dysglycaemic was predominantly impaired glucose tolerance (IGT: 77%). MetS was higher among dysglycaemic subjects although also detected in 13% of normo glycaemic subjects. Eighty percent of IGT subjects did not have MetS. Sixty-eight percent of subjects had intermediate or high CVD risks (hsCRP>1mg/L). hscRP increased with obesity and was not associated with glycaemic status. Infant birth weight, maternal age and triglycerides were independent predictors of dysglycaemia (p<0.05).

Conclusion: Despite the low prevalence of MetS, elevated levels of hsCRP among these women with prior-GDM was highly prevalent. Normoglycaemic subjects with MetS demonstrated intermediate to high risk hsCRP levels. The findings also emphasize the importance of performing OGTT mainly in older post-GDM women, with higher triglycerides and infants who are large for gestational age.

Keywords: Gestational diabetes mellitus; Type 2 diabetes; Metabolic syndrome; Cardiovascular risks; Dysglycaemia; Dyslipidaemia

Introduction

Gestational Diabetes Mellitus (GDM) which describes abnormal glucose homeostasis in pregnancy, has been recognised to increase maternal risks for the development of diabetes and Cardio-Vascular Diseases (CVD) [1,2]. Previous data has recommended early detection and management of cardio-metabolic risk factors in women post GDM [3]. Central obesity, insulin resistance, glucose intolerance, hypertriglyceridemia, high levels of inflammatory markers and low high density lipoprotein cholesterol (HDL-C) are components of metabolic syndrome (MetS) and commonly seen in women with previous GDM [4,5]. MetS predicts approximately 50% of the risk for diabetes and 25% of all new-onset CVD [6]. Hence a diagnosis of MetS in women post-GDM identifies women with increased cardio-metabolic risks who would benefit from early intervention [7].

High sensitivity C-reactive protein (hs-CRP) is an inflammatory marker recommended for risk stratification for individuals with high cardiovascular risk [8,9]. MetS is associated with high levels of hsCRP and linked to increased risk for CVD and diabetes [10,11]. This study evaluated the associations between MetS, abnormal glucose tolerance and cardiovascular risk factors in Malaysian women with prior GDM. Currently, there is a paucity of similar data for the Malaysian population.

Materials and Methods

This project was approved by the Ethics and Research Review Committees of the institutions involved consistent with the national regulations. Subjects who were diagnosed to have had GDM (WHO criteria [12]) were identified 2-6 months after delivery. The inclusion criteria were women between the ages of 20-40 years with the presence of at-least one of the following three risk factors: 1. central obesity [described as a body mass index (BMI)>23 kg/m², or waist circumference (WC)> 80 cm], 2. Dysglycaemia (Impaired glucose tolerance (IGT: 2-h plasma glucose ≥ 7.8 and <11.1 mmol/L [13]) and/

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or Impaired fasting glucose (IFG: FBS \geq 5.6 to $<$ 7.0 mmol/L [6]) values at the screening Oral Glucose Tolerance Test (OGTT) and presence of family history of diabetes. Exclusion criteria were: Subjects with type 2 diabetes (as defined by American Diabetes Association, 2007 [13]), pregnancy, and the use of drugs which may affect metabolic profiles were excluded. A total of 304 women with GDM identified from the Hospital Delivery Register were screened. Seventy-seven subjects were eligible and informed consent was obtained. All outcome measures were measured postpartum.

Subjects' body weight and height, rounded to 0.1kg and 0.1cm respectively, were measured in light clothing, without footwear and after emptying pockets. Body weight was measured using digital weighing scales (Model: BWB-800A, Tanita Corporation, Tokyo, Japan) and height using the wall-mounted stadiometer (Model No.: 206, SECA, Hamburg, Germany) and BMI was calculated. Waist (WC) and hip circumference were measured following WHO guidelines and Waist-Hip Ratio (WHR) was calculated [14]. Body fat % and trunk fat % were measured using the dual-emission X-ray absorptiometry (DEXA, Model: Delphi, Hologic Systems, Bedford, USA) as per the manufacturer's instructions.

Blood Pressure (BP) was taken in the sitting position from the left arm after a 10-minute rest, using the automatic sphygmomanometer (Colin Press Mate, Colin Medical Technology Corporation, Tokyo, Japan). An average of two consecutive readings was measured [15].

Blood samples were obtained after a 10-hour overnight fast. OGTT was performed using 75g of dextrous anhydrous glucose dissolved in 250-300ml of drinking water. Blood samples were collected pre-test and at two hours (2HPP). Blood glucose was measured using the Hexokinase/G6PD method. Triglyceride (TG) and Total Cholesterol (TC) were measured using enzymatic colorimetric method. HDL-cholesterol was assessed by homogeneous enzymatic colorimetric method. LDL-cholesterol was calculated using the Friedwald's formula. Serum samples for hs-CRP testing were stored at -20°C degrees until assayed using enzymatic system. hsCRP Values above 10 mg/L were excluded to avoid possibility of ongoing infection [16].

Definition of cardio-metabolic risks

A combination of WC $>$ 80cm, BMI $>$ 23 and body fat $>$ 35% indicate obesity with an increased risk for cardio-metabolic diseases [17]. The IDF harmonized criteria was used to define MetS [6]; i.e. presence of any three out of the following five components: 1. the presence of central obesity (for South Asian women WC \geq 80 cm, or BMI is $>$ 30 kg/m²) 2. raised TG \geq 150 mg/dl (1.7 mmol/L) 3. reduced HDL cholesterol abnormality $<$ 50 mg/dl (1.29mmol/L) in females, 4.raised BP systolic BP \geq 130 or diastolic BP \geq 85 mmHg and 5. raised fasting blood sugar (FBS) \geq 100 mg/dl (5.6mmol/L). HsCRP values were used to stratify CVD risk into three categories: "Low" (hsCRP $<$ 1 mg/L), "Intermediate" (1-3 mg/L) and "High" ($>$ 3 mg/L)[16].

Statistical analyses

Statistical analyses were performed using IBM SPSS (Version 19, Somers, NY). Normally distributed data are presented as mean SD. Median and Inter-Quartile Ranges (IQR) are presented for data that was not normally distributed. Differences between groups for continuous data were assessed by independent t-test (for normally distributed data) and nonparametric tests for data not normally distributed. Chi-square was used to analyse categorical data. Associations between variables were studied with Pearson's or Spearman's correlation co-efficient depending on the normality of the data. The statistical significance standard was set at 5%.

To investigate associations with dysglycaemia, variables were entered into a logistic regression model with presence or absence of dysglycaemia as the dependant variables. Age, number of children, number of pregnancies, birth weight of children, WHR and TG were the co-variates used in the model. Variables not substantially contributing to the model were systematically removed in a backward stepwise regression process using the likelihood ratio test as the criterion for removal. Age, baby birth weight and TG remained the significant predictors in the final model. The Hosmer-Lemeshow χ^2 test was used to assess the goodness of fit between the observed and predicted number of outcomes for the final model and $p>$ 0.05 was taken to indicate a good fit. The final model for predicting dysglycaemia had a good fit (Hosmer-Lemeshow χ^2 test p value = 0.814).

Results

The demographic and metabolic parameters are shown in Table 1. The median duration since last GDM delivery to the time of screening was 4 months (IQR 2) The majority (74%) of the subjects were Malays, followed by Chinese (17%), Indians (6%) and others (3%, including one Indonesian and one Myanmarese).

The mean BMI, body fat% and WC of the subjects were above recommended healthy limits for Asian women [17]. Overall, 17 subjects (22%) met the IDF harmonized criteria for MetS [6]. Based on the criteria, 67.5% of subjects had central obesity, 11.7% had IFG (FBS $>$ 5.6 mmol/L), 12% had TG $>$ 1.7 mmol/L, while 36% had HDL-C $<$ 1.3 mmol/L, and 24% had elevated BP [6]. Based on hsCRP CV risk stratification, 20 subjects (31.7%) were in the low risk, 25 (39.7%) in the intermediate risk and 18(28.6%) were in the high risk category [16].

Women with or without MetS, were similar in their ages (31.2 ± 4.7 vs. 31.8 ± 3.2 years, $p=0.647$, Figure 1) and family history of diabetes (82.4 vs. 83.1%, $p=1.0$) There were no differences in the total number of pregnancies, number of GDM pregnancies, number of parity, time lapse since last GDM-delivery and birth-weight of infants. However, women with MetS had earlier diagnosis of GDM during pregnancy at median of 17 (IQR 8.5) vs. 26 (8.5) weeks, $p=0.002$. The subjects who satisfied the MetS criteria had higher BMI, body and trunk fat and higher systolic and diastolic BP ($p<$ 0.05, Table 2).

Among the 77 subjects, 22 (29%) demonstrated dysglycaemia

Parameter	Mean SD
Age (y)	30.5 \pm 9
Weight (Kg)	65.1 \pm 12.1
BMI (Kg/m ²)	26.4 \pm 4.6
Waist Circumference (cm.)	83.2 \pm 8.8
Waist-Hip- Ratio	0.81 \pm 0.05
Body Fat %	38.4 \pm 5.3
Trunk fat %	37.2 \pm 6.6
Fasting Blood Glucose (mmol/L)†	4.7 \pm 0.7
2h- postprandial blood glucose (mmol/L)	6.51 \pm 1.6
Triglyceride (mmol/L)†	0.86 \pm 0.72
Total Cholesterol (mmol/L)	5.18 \pm 0.32
HDL-Cholesterol (mmol/L)†	1.43 \pm 0.43
LDL-Cholesterol (mmol/L)	3.30 \pm 0.79
Systolic BP (mmHg)†	115.5 \pm 21
Diastolic BP (mmHg)	67.4 \pm 11.7

GDM: Gestational diabetes mellitus; BP- Blood pressure;†: values not normally distributed, data presented as median (Interquartile Range (IQR))

Table 1: Demographic and Metabolic Parameters in Post-GDM Subjects without Diabetes.

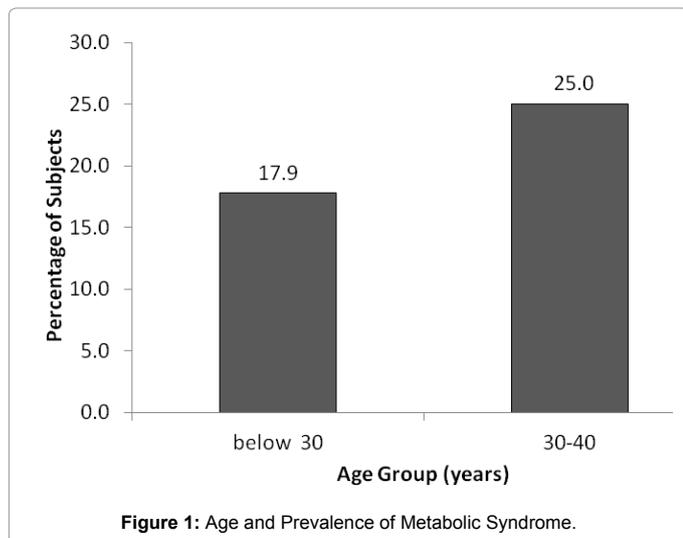


Figure 1: Age and Prevalence of Metabolic Syndrome.

Parameter	Metabolic Syndrome		P ¹ value
	Yes (n=17)	No (n=60)	
Weight (kg)	74.0 ± 11.7	62.6 ± 11.0	<0.001
BMI (Kg/m ²)	29.8 ± 4.2	25.5 ± 4.3	<0.001
WC (cm)	90.5 ± 8.4	81.1±7.8	<0.001
WHR	0.84 ± 0.05	0.80 ± 0.05	0.009
Body Fat %	41.5 ± 4.3	37.6 ± 5.3	0.009
Trunk fat %	42.3 ± 4.7	35.7 ± 6.4	<0.001
FBS(mmol/L)†	5.4 ± 0.47	4.6 ± 0.41	<0.001
2HPP(mmol/L)	7.4 ± 1.6	6.3 ± 1.4	0.005
TC (mmol/L)	5.2(1.5)	5.0(1.09)	0.418
TG(mmol/L) †	1.8(0.8)	0.76(0.37)	<0.001
HDL(mmol/L)†	1.0(0.16)	1.5(0.23)	<0.001
LDL (mmol/L)	3.2(1.28)	3.2(0.96)	0.418
TC:HDL †	5.2 (1.5)	3.3 (1.4)	<0.001
HDL:LDL †	0.3(0.1)	0.48 (0.2)	0.001
Systolic BP (mmHg) †	126 ± 17.4	116.9 ± 14.1	0.030
Diastolic BP (mmHg)	72.6 ± 12.1	65.9 ± 11.3	0.036
hsCRP	3.07 ± 2.1	2.09 ± 1.8	0.111

Abbreviations: GDM: Gestational diabetes mellitus; MetS: Metabolic syndrome; BMI: Body mass Index; WC: Waist Circumference; WHR: Waist Hip ratio; FBS: Fasting blood glucose; 2HPP: 2 hour post prandial blood glucose on OGTT test; TC: Total cholesterol; TG- Triglyceride; BP: Blood pressure; BBW: Baby birth weight Values are presented as mean ± SD, † if not normally distributed, data presented as median (interquartile range (IQR)),

P¹-comparing values across those with and without metabolic syndrome

Table 2: Comparison of Anthropometric and Metabolic Parameters of Post-GDM subjects with or without Metabolic Syndrome.

(IFG or IGT or both) and 55 (71%) had normoglycaemia. Within the dysglycaemic group, five had IFG only, 13 had IGT only and four subjects had both abnormalities. The demographic and metabolic parameters of the two groups are shown in Table 3. Subjects with dysglycaemia were significantly older (33.9 ± 3.9 vs. 30.3 ± 4.2 years, $p=0.003$), reported a higher number of pregnancies (mean (SD) 2.7(1.3) vs. 2.0(1.4), $p=0.025$) and had more children (mean (SD) 2.4(1) vs. 1.97(1.2), $p=0.028$) compared to those with normoglycaemia (Refer Table 3). Subjects with dysglycaemia had significantly higher WHR (0.83 ± 0.05 vs. 0.80 ± 0.05 , $p=0.037$) and TG levels (median (IQR): 1.3(1.02) vs. 0.72(0.26), $p=0.005$) compared to those with normoglycaemia (Table 3). The dysglycaemic group had more subjects with high TG >1.7mmol/L

(24% vs. 7%, $p=0.105$) and low HDL-C <1.29 mmol/L (52% vs. 29%, $p=0.067$). The dysglycaemic group demonstrated a higher prevalence of MetS in comparison to the normoglycaemic group (48% vs. 13%, $p=0.001$). All subjects who had both IFG and IGT met the criteria for MetS, in comparison to 80% of those with only IGT and 15.4% of those with only IFG (Figure 2). The dysglycaemia group had more MetS

Parameter	Normoglycaemia (n= 55)	Dysglycaemia (n= 22)	P ¹
Age (y) †	30.3 ± 4.2	33.9 ± 3.9	0.001
No. of Pregnancies	2.7 (1.3)	2.0(1.4)	0.025
No. GDM Pregnancies †	1.00 (0)	1(1)	0.066
Parity	2.4 (1)	1.97(1.2)	0.028
GDM identified (month of pregnancy)†	6.0 (2)	4.5(3)	0.277
Baby birth weight (kg)	3.1±0.38	3.3±0.43	0.022
Weight (kg)	63.6± 11.8	68.9±12.2	0.083
BMI (kg/m ²)	25.9±4.6	27.8±4.5	0.108
WC (cm)	81.9±1.2	86.5±1.7	0.037
WHR	0.80±0.05	0.83±0.05	0.037
Body Fat %	38.2±5.6	39.0±4.7	0.592
Trunk fat %	36.6±6.9	38.8±5.7	0.213
FBS (mmol/L) †	4.6 ± 0.41	5.2±0.52	0.0001
2HPP (mmol/L)	5.87±1.1	8.1±1.4	<.0001
TG (mmol/L) †	0.72 (0.26)	1.3(1.02)	0.005
TC (mmol/L)	5.2(0.79)	5.1 (0.95)	0.794
HDL_C (mmol/L) †	1.4 (0.22)	1.2 (0.67)	0.146
LDL-C (mmol/L)	3.3±0.76	3.3±0.88	0.832
TC/HDL †	3.7 ± 1.11	4.24 ± 1.02	0.082
HDL/LDL †	0.48 (0.2)	0.36 (0.2)	0.133
Systolic BP (mmHg) †	117 ± 14.7	123.8 ± 16.1	0.077
Diastolic BP (mmHg)	66.2±11.6	70.1±11.8	0.120
hsCRP(mg/L)	2.0±2.38	1.24±2.48	0.844

Abbreviations: GDM: Gestational Diabetes Mellitus; BMI: Body mass Index; WC: Waist Circumference; HC: Hip circumference; WHR- waist Hip ratio; FBS: Fasting blood sugar; 2HPP: 2 hour post prandial blood glucose on OGTT test; TG: Triglyceride; TC: Total cholesterol; BP: Blood pressure; P¹-comparing values across normal and abnormal glucose tolerance (IFG, IGT, and IFG+IGT), values are presented as mean ± SD, †- if not normally distributed, data presented as median (Interquartile Range (IQR))

Table 3: Demographics and Metabolic Parameters of Subjects Post-GDM with Normoglycaemia and Dysglycaemia.

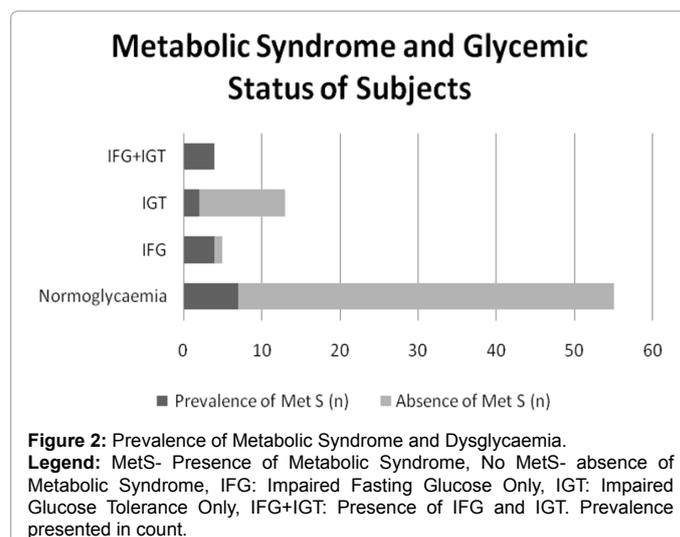


Figure 2: Prevalence of Metabolic Syndrome and Dysglycaemia. Legend: MetS- Presence of Metabolic Syndrome, No MetS- absence of Metabolic Syndrome, IFG: Impaired Fasting Glucose Only, IGT: Impaired Glucose Tolerance Only, IFG+IGT: Presence of IFG and IGT. Prevalence presented in count.

criterion compared to the normoglycaemic group (median: 3 (IQR 2) vs. 1(IQR 2), p=0.006)

Logistic regression analysis showed that infant birth weight, TG and age were significant independent predictors of postpartum dysglycaemia among this post-GDM cohort (OR: 8.723, p= 0.018; OR= 5.56, p=0.008; and OR=1.29, p=0.002, respectively).

Among subjects diagnosed with MetS, 18.2, 36.4 and 45.5% of subjects were in the low, intermediate and high hsCRP risk strata. Among subjects without Met S, 34.6, 40.4 and 25% of the subjects were in the low, intermediate and high hsCRP risk strata. There was no significant trend associating presence of Met S with higher hsCRP levels (p=0.343). hscRP levels did not vary significantly between

No. of MetS criteria satisfied*	Dysglycaemia % of subjects	Normoglycaemia % of subjects
0	14.2	36.4
1	14.2	27.3
2	24.8	23.6
3	38.1	12.7
4	9.5	0

* Difference in distribution between groups p< 0.001

Table 4: Metabolic Syndrome criteria in post-GDM women with and without dysglycaemia.

	hsCRP CV risk categories			p Value
	Low	Intermediate	High	
Weight (kg)	53.6(10)	65.8 (13)	68.5(16)	<0.001
BMI	21.6(4.6)	26.3(4.7)	28.2(6.3)	<0.001
WC cm	77 ± 6.7	82.5 ± 6.9	86.6 ± 5.3	<0.001
Body Fat %	33 ± 5.1	37.7 ± 6.2	41.7 ± 3.8	<0.001
Trunk fat %	30.1 ± 6.5	36.5 ± 4.4	40.8 ± 3.4	<0.001
TC	5.3 ± 0.9	4.9 ± 0.8	5.0 ± 0.87	0.04
HDL	1.5(0.32)	1.37(0.27)	1.38(0.38)	0.035
No. of MetS Components	0(1.5)	1(2)	2(1.5)	0.002

Abbreviations: GDM: Gestational Diabetes Mellitus; BMI: Body mass Index; WC: Waist Circumference; TC: Total cholesterol, P[†]: comparing values across the hsCRP risk categories, values are presented as mean ± SD, † - if not normally distributed, data presented as median (interquartile range (IQR))

Table 5: HighsensitivityC-reactive protein (hsCRP) based risk and metabolic outcomes of interest.

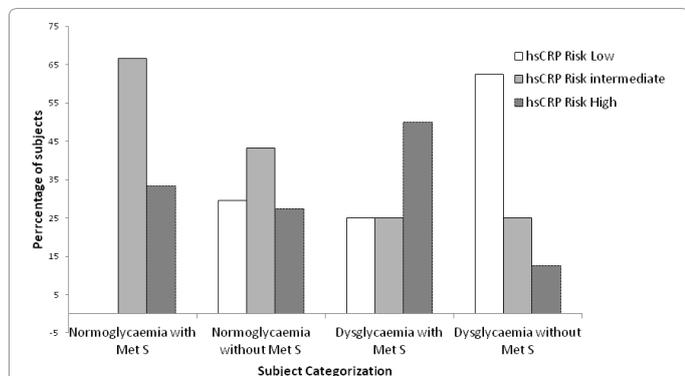


Figure 3: hsCRP Risk Stratification and Presence of Dysglycaemia and Met S among Post-GDM Women.

Legend: MetS- Metabolic Syndrome, hsCRP: high sensitivity C - reactive protein. HsCRP values based CVD risk stratification: "Low" (hsCRP<1mg/L), "Intermediate" (1-3mg/L) and "High" (>3mg/L) [16].

Correlation with time of GDM diagnosis		
Parameter	r *	P value
Weight	-0.246	0.037
WC	-0.295	0.012
Hip	-0.274	0.020
BMI	-0.307	0.009
Total Body Fat%	-0.259	0.034
Trunk Fat%	-0.310	0.010
FBS	-0.238	0.044
2HPP	-0.29	0.013
TG	-0.374	0.001
Systolic BP	-0.287	0.015
Diastolic BP	-0.301	0.011
HDL-C	0.318	0.007
TC: HDL	-0.30	0.009
LDL:HDL	-0.287	0.015
MetS Diagnosis	-0.367	0.002
Presence of Dysglycaemia	-0.129	0.280
Total no. of Metabolic Risks	-0.468	<0.001
hsCRP	0.202	0.112

r * - Spearman's correlation coefficient

Abbreviations: WC: Waist Circumference; BMI: Body mass Index; FBS: Fasting blood sugar; 2HPP: 2 hour post prandial blood glucose on 75g OGTT test; TG: Triglyceride; TC: Total cholesterol; BP: Blood pressure; MetS: Metabolic Syndrome

Table 6: Association between Time of GDM Diagnosis during Pregnancy and Postpartum Metabolic Parameters.

subjects with and without MetS (3.07 ± 2.1 vs. 2.09 ± 1.8mg/L, p=0.111, Table 2).

Subjects in the high hsCRP category >3 mg/L were significantly heavier, had increased WC, body and trunk fat with lower HDL-C levels (Table 5). Regression analysis showed that for every 5% increase in total body fat, there was an increase of hsCRP by 1.05 mg/L.

The mean FBS in subjects in the low, intermediate and high hsCRP risk categories were similar (4.7 ± 0.5, 4.5 ± 0.5 and 4.8 ± 0.6 mmol/L, respectively p= 0.785). The 2HPP in these hsCRP risk strata also showed no significant difference (6.7 ± 1.8, 6.1 ± 1.7 and 7.0 ± 1.3 mmol/L, respectively, p=0.165). Median hsCRP levels were comparable between subjects with and without dysglycaemia (median 1.7 (IQR 3.5) vs. 1.5(IQR 2.5) mg/L, p=0.844).

The percentage of subjects within the different hsCRP categories, glucose tolerance and Met S status are illustrated in Figure 3. The group with MetS and dysglycaemia revealed the highest percentage of subjects within the high risk hsCRP category. However, subjects with normoglycaemia but who met sufficient criteria for MetS were all within the intermediate and high hsCRP CV risk categories. Furthermore approximately 70% of the normoglycaemic subjects without MetS were in intermediate and high hsCRP CV risk categories.

The time of GDM diagnosis during pregnancy showed small but significant negative correlation with postpartum anthropometric measures, glycaemic variables, TG, BP and MetS diagnosis (Table 6). Overall, 82% of the subjects had a family history of diabetes. Subjects with family history of diabetes had higher TC (median 5.18 vs. 4.89 mmol/L, p=0.019), TC: HDL ratio (median 3.82 vs. 3.29, p=0.043) and LDL- cholesterol (mean 3.39 vs. 2.86 mmol/L, p=0.027) levels. Both the dysglycaemic and the normoglycaemic groups had similar prevalence of family history of diabetes (78.2 vs. 90.9%, p=0.325)

Discussion

This study demonstrated a prevalence of MetS at 22% among high-risk Post-GDM women at a median postpartum duration of 4 months. The prevalence was comparable to the 20% MetS prevalence reported among Canadian GDM women at three months postpartum [7]. The IDF harmonized criteria which included the presence of central obesity as one of the five criteria to diagnose MetS was used in this study. To validate the use of this criterion in early postpartum, when there may be some retention of weight gained during the pregnancy [18], we performed a sensitivity analysis which was similar to the approach documented in an earlier study conducted among Canadian Post-GDM women at 3-months postpartum [7]. The sensitivity analysis excluded the criterion for central obesity and defined MetS by the presence of two of the four other MetS components. The results of sensitivity analysis indicate that MetS diagnosis in the early postpartum period (2-6months postpartum) is not affected by post-delivery weight retention and after this adjustment, the prevalence of 22% remained unaltered. However, larger cross-sectional studies are needed to confirm the validity of using MetS criteria in early postpartum.

Despite the concern on residual postpartum weight and waist circumference and by the inclusion criterion of this study including high-risk subjects, our observation was notably low in comparison to previously reported 2-3 fold increase in MetS prevalence among post GDM-women as compared to those with normal pregnancies [7,19,20]. The 22% MetS prevalence in our study group was similar to the figure reported in a population of healthy women in the North-Eastern part of the country (24%). This relatively high prevalence within the latter cohort may partly be due to the inclusion of older women as the age range was noticeably wider (30-57 years old) [20]. Furthermore, the national estimate of MetS among adult females, which include a wider age range of between 18-70 years of age, for the country is 33.1% [21].

All subjects with both IFG and IGT met the criteria for MetS and almost half of those with either IFG or IGT had the same diagnosis. However, within the normoglycaemic group, 13% of the subjects were found to have MetS which was predominantly contributed by low HDL levels (n=7), hypertriglyceridemia (n=4) and elevated BP (n=3). These findings suggest an added role of diagnosing MetS normoglycaemic women as it identified increased cardiovascular risks in a sub-group that would otherwise be overlooked due to their younger age and normoglycaemic status. This is further supported by the hsCRP levels, which indicate that despite being normoglycaemic all subjects who had MetS were within the intermediate and high risk categories.

Subjects with dysglycaemia had an expected higher prevalence of MetS in comparison to those with normoglycaemia (48% vs. 13%, $p=0.001$). However, dysglycaemic subjects who did not have MetS seemed to be predominantly those with IGT only (n=11/13) (Figure 2). This observation could be largely attributed to the MetS diagnostic criteria which utilises IFG to qualify glucose intolerance rather than IGT, the latter being the more commonly detected in GDM [3]. This is proven within the study cohort, which showed prevalence of IGT being almost three times more common than IFG. These observations may suggest the importance of performing OGTT postpartum to evaluate postprandial dysglycaemia in the absence of IFG in post GDM women. A Met S diagnosis using the fasting glucose levels may not satisfactorily capture the prevalent abnormal glucose tolerance among women post-GDM.

Our data demonstrated an increase in the prevalence of dysglycaemia with age, which is consistent with a Canadian post-GDM cohort [22]. The increased prevalence of dysglycaemia among older subjects can

be expected as insulin resistance increases with age [23]. Logistic regression analyses found that for every one year increase in maternal age among the study subjects there was an associated 25% higher risk for developing postpartum dysglycaemia. Maternal postpartum dysglycaemia was also significantly associated with higher infant birth weight. Logistic regression analysis showed that infant's birth weight was a significant independent predictor of postpartum dysglycaemia in the mother. This finding reaffirms earlier studies which demonstrated Asian women who gave birth to infants with heavier birth weight are more likely to develop insulin resistance [24]. Therefore, our data emphasized the importance of evaluating postpartum dysglycaemia among older women with GDM and those with heavier infants [22].

Insulin resistance, higher body weight, WC and body fat are associated with higher hsCRP levels which is further linked to increased inflammatory state [16]. Hence, it was not surprising that a large proportion of our GDM subjects had $hsCRP > 1$ mg/L. The large Diabetes Prevention Study (DPP) study revealed moderate weight loss through lifestyle intervention resulted in a reduction of hsCRP by 29% (i.e. ≈ 0.5 mg/L) which persisted without further weight loss. Hence, lifestyle changes or behavioural therapy aiming for weight loss among post-GDM subjects will have an added benefit of lowering hsCRP levels in those with higher levels of this inflammatory marker [25]. It is acknowledged that while several interventions both pharmacologic and lifestyle modification have shown to lower hsCRP levels, the impact of the reduction on clinical outcomes remains to be convincingly established [26].

There was no significant correlation between the diagnosis of MetS and hsCRP levels. Furthermore, within the normoglycaemic subjects without Met S, more than a quarter (27.3%) had $hsCRP > 3$ mg/ml. Therefore, this may suggest that MetS is insufficient to identify the complete spectrum of cardiovascular risk in post-GDM subjects and hsCRP may provide further information on residual CVD risks.

Earlier diagnosis of GDM during the ante-natal period was significantly associated with postpartum central obesity, dysglycaemia, higher BP, dyslipidaemia and MetS diagnosis. This is consistent with reports from earlier studies [18]. Family history of diabetes was associated with higher TC, TC: HDL ratios and LDL- cholesterol, which confirmed similar findings from Italy and Gambia [27,28].

Correlation analysis showed higher TG levels to be associated with postpartum dysglycaemia and with every 1 mmol/L increase in TG there is a two-fold increase in the odds ratio for postpartum dysglycaemia which is similar to data collected among Korean Post-GDM women [29]. This further strengthens the associations between increased body weight, insulin resistance and postprandial glucose metabolism in the development of cardio-metabolic risks [30]; and emphasizes the need for glucose tolerance evaluation.

The current study was limited by the small sample size and confined to single-centre recruitment. Nevertheless, the results have provided evidence on the importance of detecting abnormal glucose tolerance and CV risk assessment in Post-GDM women within the reproductive age.

In conclusion, we demonstrated that MetS is a relevant diagnosis to detect in normoglycaemic post-GDM women. Subjects with abnormal glucose tolerance (IFG or IGT or both) had expectedly higher prevalence of MetS but a small proportion (13%) of subjects with normoglycaemia met the diagnosis as well. Postpartum MetS screening did not predict postpartum IGT which strongly suggests the importance of OGTT in the absence of IFG to rule out glucose intolerance. Maternal age, infant birth weight and TG were independent predictors of postpartum

dysglycaemia. Dysglycaemia, earlier GDM diagnosis and family history of diabetes were associated with increased cardiovascular risks.

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Location of the Study and Ethics Approvals

The study was conducted at the Endocrinology Unit of Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, Malaysia. The project was approved by Ethics and Research Review Committee of International Medical University, Kuala Lumpur and the Research Committee of UKMMC. The study is registered with Malaysian National Medical Research Register (NMRR) with the Research ID: 5183.

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