## Validation of a New Diagnostic Index to Determine Metabolic Obesity Phenotypes in Normal-Weight Women in Early Pregnancy

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### ABSTRACT

**INTRODUCTION** It would be useful to have diagnostic indices for obesity phenotypes in pregnant women based on morphological traits and the specific distribution of abdominal adipose tissue. This type of practical resource would allow for the classification of obesity phenotypes in normal-weight women in early pregnancy and would contribute to primary healthcare followup of pregnant women.

**OBJECTIVE** Validate a new diagnostic index for the metabolically unhealthy obese, normal-weight phenotype, as a determinant for cardiometabolic risk in normal-weight pregnant Cuban women in the first trimester of pregnancy.

**METHODS** A cross-sectional study of 526 pregnant women at a gestational age of 12 to 14 weeks seen at the ultrasound service of the Chiqui Gómez Lubián Teaching Polyclinic, Santa Clara municipality, Villa Clara province, Cuba, was conducted from January 2016 through July 2020. Subcutaneous, preperitoneal and visceral abdominal fats, as well as anthropometric and blood chemistry variables, were measured. The women were divided into three groups based on metabolic phenotypes, taking into account body mass index in the normal weight range, visceral adiposity index values and the lipid accumulation product starting at the 75th percentile.

### **INTRODUCTION**

Consensus is lacking on clinical management of obesity during pregnancy as there is not consistent evidence justifying one or another change in this regard. The prominence of adipose tissue in the genesis of metabolic and cardiovascular complications related to obesity[1] has increasingly drawn interest to the differentiation between specific adipose tissue depots due to their association with obesity phenotypes that contribute to development of type 2 diabetes and cardiovascular disease.[2]

The body's response to central adiposity is complex. Under conditions of obesity, visceral adipose tissue becomes the first store of triglycerides when faced with the inability of subcutaneous adipose tissue to store such excess energy ('overflow hypothesis'), which causes lipotoxicity and insulin resistance (IR). According to some researchers, subcutaneous adipose tissue is related to

**IMPORTANCE** Based on ultrasound measurement of abdominal fat, an index was obtained to diagnose an unhealthy (metabolically obese, normal-weight) phenotype in early pregnancy, facilitating identification and prevention of cardiometabolic risk in pregnant women.

The new index, called the abdominal adipose deposit index, was obtained by multiplying the subcutaneous fat thickness by visceral fat thickness, both measured by ultrasound. A cutoff point was established that facilitated discernment of an unhealthy phenotype: normal weight but metabolically obese, a cardiometabolic risk factor.

**RESULTS** Receiver operating characteristic (ROC) analysis of the abdominal adipose deposit index to distinguish the metabolically unhealthy obese, normal-weight phenotype in normal-weight pregnant women showed an area under the curve of 0.707 (95% CI: 0.62–0.79, p <0.001), greater than that of the body fat index (0.630; 95% CI: 0.54–0.72), the fat accumulation index (0.637; 95% CI: 0.55–0.73) and other established ultrasound indices of abdominal adiposity, with a prevalence of 6.3%.

**CONCLUSIONS** The abdominal adipose deposit index is better than other traditional indicators at detecting the risk of metabolic obesity in early pregnancy in normal-weight women, facilitating early intervention in clinical practice to prevent or delay progression of cardiometabolic disease in these women.

**KEYWORDS** Abdominal adipose tissue, abdominal fat, pregnant woman, phenotype, metabolic syndrome, diagnostic ultrasound, Cuba

and influences IR, at least as much or more than perivisceral adiposity. Subcutaneous adipose tissue possesses a considerably higher adipose mass, which influences insulin sensitivity due to the volume of free fatty acids that it sends into general circulation, considered an insulin resistance phenomenon via a non-portal mechanism.[3,4]

The essential mechanism for development of metabolically abnormal phenotypes is disruption in the ability of subcutaneous tissue adipocytes to proliferate and differentiate, which leads to a limitation of adipocyte hyperplasia and to adipocyte hypertrophy, with an increase in the flow of fatty acids to the visceral adipose tissue and consequent accumulation of fat in other ectopic tissues. This represents an emerging clinical problem that in the near future may materialize as higher rates of 'healthy obese' and 'thin sick' individuals, which require coordination of diagnostic criteria on metabolic phenotypes with other studies that examine the relevance of the various definitions and findings.[5]

During pregnancy, when waist circumference is changing significantly, different criteria have been used to classify metabolic syndrome (MetS). Its high prevalence, the metabolic risks caused by the physiological changes of pregnancy and postpartum, the lack of indicators to classify the syndrome, as well as inconsistencies regarding its prevalence and associated factors in women with no prior diseases, support the need for research on the subject.[6]

The US National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria,[7] which include abdominal obesity as an independent risk factor for cardiometabolic disease,[8] have been used to predict MetS in pregnant women due to the simplicity of their application.

Few studies have researched central adipose tissue deposits and glucose homeostasis in pregnancy.[9] An obese woman has a metabolic increase of IR in early pregnancy, with results such as glucose intolerance and fetal overgrowth, that clinically manifest in late pregnancy. While a single mechanism has not been identified to explain the adverse perinatal results associated with maternal obesity, nonetheless maternal pregestational insulin resistance, inflammation and oxidative stress could contribute to early placental insufficiency.[10]

Ultrasonography has often been used as a necessary substitute for waist circumference measurements during pregnancy. [11] These measurements, together with the usual first trimester ultrasound examination, may provide additional information more useful than body mass index (BMI) regarding association with cardiometabolic risk factors and IR.[12]

Evidence shows that ultrasonographic indices of abdominal adiposity, such as abdominal fat index (AFI),[13] fat accumulation index (FAI),[14] body fat index (BFI)[15] and others, combined with use of anthropometric measurements and laboratory studies such as visceral adiposity index (VAI),[16] are better cardiometabolic risk indicators than BMI. However, despite the existence of cutoff points that appear optimal for diagnosing obesity and MetS, studies in several countries and ethnic groups have arrived at different conclusions.[17] No single definition exists for the metabolically obese phenotype in a normal-weight pregnant woman. This makes it difficult to compare results[18] or to apply them to the Cuban population, least of all to pregnant Cuban women.

There are no studies on abdominal adiposity using ultrasound (US) in Cuba, despite its wide availability in our healthcare institutions, and thus its potential to diagnose obesity has not yet been reached, particularly in early pregnancy.

Considering that some cardiometabolic risk factors can be identified using obesity phenotypes,[19] creating a new abdominal adipose deposit index (AADI) based on direct measurement of subcutaneous and visceral fat using US and its validation in the first trimester of pregnancy, would provide an instrument for early differentiation of such risks in this population group,[6,20,21] and would support a new clinical approach for managing obesity and its implications during pregnancy.

The objective of this study was to validate a new diagnostic index to determine a metabolically-unhealthy and obese phenotype in normal-weight pregnant women in Cuba, as an indicator of cardiometabolic risk in early pregnancy.

### **METHODS**

**Design and population** A cross-sectional study was conducted with 2357 women of all nutritional statuses in the first trimester of

pregnancy from various community polyclinic catchment areas in Santa Clara municipality, Villa Clara province, Cuba, seen at the Prenatal Ultrasound Service of the Chiqui Gómez Lubián Teaching Polyclinic, from January 2016 through June 2020. The study population comprised 526 pregnant women after applying the following criteria:

*Inclusion criteria* Classified as normal weight according to BMI, aged 20–35 years, pregnant with a single fetus and at a gestational age of 12–14 weeks (confirmed by US).

*Exclusion criteria* Presence of metabolic disease including diabetes mellitus in any of its stages, dyslipidemia, psychiatric disorders, uterine fibroids and regular consumption of prescription drugs.

*Exit criteria* Termination or loss of pregnancy and incomplete or unreliable data.

### Study variables

Ultrasound variables and their determination Thickness in millimeters (mm) of subcutaneous abdominal fat (SAF), preperitoneal fat (PPF) and visceral fat (VF) were measured by US. SAF was measured in the upper half of the anterior abdominal wall above the umbilicus, for which a longitudinal scan was done perpendicular to the skin, at the lowest point between the wall and the linea alba at the level of the xiphoid process. PPF was measured at the maximum point, behind the anterior abdominal wall and at the level of the xiphoid process, between the linea alba and the peritoneum that covers the liver surface, placing the transducer perpendicular to the skin. SAF thickness was obtained by placing the electronic cursors located in the skin-fat interface (excluding the skin) to the linea alba; to measure PPF thickness, cursors were placed in the fat-muscle interface, between the linea alba and the liver surface, keeping them almost parallel to the skin, according to the Suzuki technique.[13] To measure VF, cursors were placed at the internal edge of the rectus abdominis muscle, without including it, and at the anterior edge of the spine, at the level of the fourth lumbar vertebra (L4-L5), placing the transducer between one and two centimeters above the umbilicus, according to Armellini.[22] No standardized cutoff points or reference values have been reported for these variables in pregnancy.

Abdominal adipose deposit index (AADI) The new index proposed in this study was obtained by multiplying the thickness of the subcutaneous fatty tissue by the thickness of visceral fatty tissue, both measured by ultrasound: AADI = SAF × VF. The AADI result is expressed in mm<sup>2</sup> and includes both fatty depots, which are anatomically and functionally related in their metabolic effects. The creation of this index is supported by theories on the accumulation of abdominal adipose tissue that suggest that the maximum expansion capacity of SAF leads to accumulation of VF, which has been associated with various cardiometabolic risk factors. When the superficial subcutaneous compartment reaches its full capacity for fat storage, the secondary depots, such as the deep subcutaneous and visceral depots, assume the main role in the accumulation of the excess triglycerides, manifested in an increase of the values of this index. As will be indicated later. the cutoff point for the AADI was established at 350 mm<sup>2</sup>. Values above this threshold identified the metabolically obese, normalweight phenotype in pregnant women.

*Fat accumulation index (FAI)* Calculated as the sum of SAF and PPF.[14]

Anterior abdominal wall adiposity index (simplified to abdominal fat index, AFI) Calculated as the quotient between PPF and SAF. [14]

*Body fat index (BFI)* Calculated by the equation: BFI = (PPF × SAF)/Height.[15]

Anthropometric variables Weight (kg) and height (m) were measured for the BMI calculation when the pregnancy was reported; if a pregnant woman had a value 18.8–25.6 kg/m<sup>2</sup> she was classified as normal weight, according to the Anthropometric Pregnancy Tables (one of which is Cuban).[23,24] Waist circumference (WC) was considered a risk indicator at >88 cm.[25]

*Blood chemistry risk variables* Blood glucose (BG)>4.4 mmol/L,[26] triglycerides (TG) >1.7 mmol/L and high-density lipoprotein cholesterol (HDLc) <1.3 mmol/L.[25]

Combined variables (combination of blood chemistry and/or anthropometric variables) The lipid accumulation product (LAP) and the visceral adiposity index (VAI) were used,[18] for which risk variables were established starting at the 75th percentile of the study population.

All study variables were continuous quantitative variables.

**Procedures** A high-resolution Sonoacer5 scanner (Samsung Medison Co., Ltd, South Korea) was used for ultrasound measurement of abdominal fat. Measurements were taken by the same specialist—a professional in imaging technique with training in fetal echocardiography and over 15 years' experience in prenatal US diagnosis. The transducer was placed perpendicular to the skin, after exhalation, with the woman in supine decubitus position, arms at her sides. The defined area from the xifoid process to two centimeters above the umbilicus on the xifo-umbilical line was covered in conductive gel.

To validate AADI, the criteria proposed by the NCEP-ATP III[7] were used as the reference standard test,[27] modifying the cutoff point for blood glucose, with >4.4 mmol/L considered a risk value for pregnant women, according to the Second Cuban Consensus on Diabetes and Pregnancy.[26]

Panel III was selected as reference criteria for AADI validation since there are no risk criteria or standardized cutoff points associated with abdominal obesity and MetS in pregnant women in Cuba. Thus, the rest of the variables were evaluated according to Panel III criteria, also used in the Cuban guide for diagnosis, evaluation and treatment of hypertension.[25] Such criteria, in addition to their simplicity and applicability in the clinical context, have been used successfully by various authors to diagnose MetS in early stages of pregnancy.[6,20,21]

To evaluate AADI's discriminant ability to detect the metabolically obese, normal-weight phenotype (MONW), as well as MetS, we turned to the Receiver Operating Characteristic (ROC) curve. AADI was used as a contrast variable (test variable), and qualitative variables were selected from the group as explanatory variables, which were assigned numeric values to identify phenotypes or the respective presence or absence of MetS.

The study population was stratified by taking into account BMI values in the normal weight range,[23] and VAI and LAP values starting at the 75th percentile, according to the criteria of Du,[18] including the metabolically healthy obese, normal-weight phenotype (MHONW) as a transition phenotype,[3] resulting in the following groups of metabolic phenotypes:

- Metabolically healthy, normal weight (MHNW): 18.8 ≤BMI ≤ 25.6 kg/m² and VAI <2.37,
- Metabolically healthy obese, normal weight (MHONW): 18.8 ≤BMI ≤25.6 kg/m² and VAI ≥2.37,
- Metabolically unhealthy obese, normal weight (MUONW): When criteria for the MHONW phenotype are met and they also have LAP values ≥55.1.

A cutoff point was calculated seeking a balance between sensitivity and specificity, in keeping with the aim of the diagnostic test to identify the highest number of pregnant women with the MUONW phenotype or MetS, as appropriate.

To carry out the validation process, the study population of 526 pregnant women was stratified into two groups, according to presence or not of MetS, based on the modified NCEP-ATP III criteria for the blood glucose cutoff point. A pregnant woman was considered to have MetS if she met three or more of the following conditions: waist circumference >88 cm; fasting glucose >4.4 mmol/L; HDL cholesterol <1.30 mmol/L; triglycerides >1.7 mmol/L and systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg.[7]

**Statistical analysis** Information was processed with the IBM SPSS Statistics version 22.0 for Windows and Statgraphics Centurion XV professional software packages.

Analysis of variance (ANOVA) was conducted, and when the null hypothesis that the means are equal was rejected, comparisons were made a posteriori (post hoc) to which Fisher's least significant difference (LSD) method was applied to identify groups that differed among them.

Summary measures were used to describe quantitative variables, measures of central tendency, dispersion and location (mean and standard deviation, SD) for data with symmetrical distribution, and median and interquartile range (IQR) for non-symmetrical distributions. For qualitative variables, the frequency distributions expressed in absolute and relative values (number and percentage) were calculated.

For all hypothesis testing performed, p value = 0.05 was considered the threshold for statistical significance. Results were presented in tables and figures.

**Ethics** Written informed consent was provided by all participants, and the anonymity of their personal and clinical data protected. The research was approved by the Chiqui Gómez Lubián Teaching Polyclinic's Ethics Committee.

### RESULTS

Table 1 shows AADI in normal-weight pregnant women who were the subject of the study, based on their metabolic phenotypes. Prevalence of MUONW phenotype was 6.3%.

Through ANOVA analysis, significant differences in AADI were verified between phenotype groups, and an F-distribution value of 10.16 was obtained with an associated p value ≤0.001; likewise, the post hoc multiple range tests by Fisher's LSD method generated statistically significant differences among all phenotype groups.

Table 1: Descriptive statistics of the abdominal adipose deposit index (AADI) in each metabolic phenotype

	MHNW (n = 393) 74.7%	MHONW (n = 100) 19.0%	MUONW (n = 33) 6.3%
Mean (mm <sup>2</sup> )	389.71ª	435.64 <sup>b</sup>	531.52°
Standard deviation	191.23	172.08	180.06
Minimum value	73.10	96.60	184.30
Maximum value	1196.00	957.60	949.96

<sup>a.b.c</sup>Different superscripts identify groups that differ from each other, according to Fisher's LSD test (F-distribution = 10.16 and p  $\leq$ 0.001)

MHNW: Metabolically healthy, normal-weight phenotype; MHONW: Metabolically healthy obese, normal-weight phenotype; MUONW: Metabolically unhealthy obese, normal-weight phenotype

# Figure 1: ROC curves of ultrasound indicators to distinguish the metabolically unhealthy obese, normal-weight (MUONW) phenotype in normal-weight pregnant women studied



AADI: Abdominal adipose deposit index; AFI: Abdominal fat index; AUC: Area under the curve; BFI: Body fat index; FAI: Fat accumulation index; 95% CI: 95% confidence interval

**Discriminant capacity of AADI** Figure 1 presents the ROC curve which showed the greatest area under the curve for AADI (0.707; 95% CI: 0.62–0.79, p <0.001).

The cutoff point selected to detect the MUONW phenotype corresponded to an AADI value of 350 mm<sup>2</sup>, located in the graph of Figure 1 at the coordinates Sensitivity = 0.879 (87.9% correctly diagnosed pregnant women) and 1–Specificity = 0.558 (55.8% false positives).

Table 2 shows the prevalence of MetS, as well as the descriptive statistics of the US variables in study participants.

When the Panel III criteria modified to identify MetS in pregnant women were applied as the gold standard, it was confirmed that 62 had MetS (11.8%), in whom a highly significant AADI increase was observed as an expression of increased abdominal adiposity (Table 2).

In the ROC curve (Figure 2) used to evaluate the discriminant ability of the AADI to detect MetS, the area under the curve was 0.705(95% CI: 0.57–0.78), with a standard error of 0.064 and p = 0.003.

AADI's cutoff point was calculated at 350 mm<sup>2</sup>, for presence of MetS, identified at coordinates 0.457 and 0.781 on the x- and y-axes, respectively, corresponding to 78.1% of participants with correct diagnosis of MetS and 45.7% false positives.

**Diagnostic test** The contingency table (Table 3) shows the crossclassification between modified MetS based on NCEP-ATP III criteria and AADI with its cutoff point.[28]

### DISCUSSION

Prevalence of the MUONW phenotype in normal-weight pregnant women was 6.3%, coinciding with the highest AADI values among all women studied. These results show that some pregnant women, despite classification as normal weight, exhibit increased abdominal adiposity along with an underlying metabolic abnormality.[2] This phenomenon has been noted by other authors such as Ahmadi, who detected MetS in 5.3% of nonobese women in the first trimester of pregnancy based on US evaluation of visceral fat thickness.[20] Pinto Lima reported a 3.0% prevalence of MetS in early pregnancy according to Panel III criteria, also using anthropometric measures, blood pressure, metabolic profile, and US measurements of SAF and VF thickness.[6]

The different capacity of the SAF to store triglycerides and the uncontrolled and growing flow of free fatty acids to other tissues with ectopic fat deposit and lipotoxicity are evident in the MUONW phenotype. This demonstrates that such a fat layer is not an inert depot, but rather can contribute to the pathogenesis of IR with greater circulation of cytokines and free fatty acids, elevating risk of complications during pregnancy.[29]

Research on subcutaneous adipose deposits and IR in nonpregnant women emphasizes the superficial and deep compartments of the subcutaneous fat layer and describes two histologically unique tissues separated by a discrete fascial plane. The fact that the thickness of the deep subcutaneous tissue layer varies with obesity and has been shown to be a better predictor of IR than usual indicators would explain that in phenotypes classified as normal weight by their BMI, but which are actually obese due to their abdominal adipose tissue distribution, the layer of deep subcutaneous adipose tissue reveals

# Table 2: Prevalence of modified metabolic syndrome anddescriptive statistics of the ultrasound variables in normal weightpregnant women

	Modified metabolic syndrome			
Variable	Absence (n = 464) 88.2%	Presence (n = 62) 11.8%		
	Means (SD)ª an	d Medians (Q1–Q3) <sup>b</sup>		
SAF	11.28 (3.69)	13.39 (3.61)		
PPF	10.60 (8.43–12.7)	10.00 (8.73–12.88)		
VF	34.43 (9.35)	35.25 (9.62)		
AFI	0.908 (0.72–1.14)	0.793 (0.72–0.92)		
FAI	21.70 (8.03)	23.97 (5.47)		
BFI	0.766 (0.38)	0.91 (0.40)		
AADI	398.31 (188.7)	474.88 (190.12)		

<sup>a</sup>Standard Deviation (SD); <sup>b</sup>Interquartile Range (IR)

AADI: abdominal adipose deposit index; AFI: Abdominal fat index; BFI: Body fat index; FAI: Fat accumulated index; PPF: Preperitoneal fat; SAF: Subcutaneous abdominal fat; VF: Visceral fat

Figure 2: ROC curve for the abdominal adipose deposit index (AADI) to identify metabolic syndrome (MetS) in normal-weight pregnant women studied



AADI: Abdominal adipose deposit index; AUC: Area under the curve; 95% CI: 95% confidence interval

a differentiation in metabolic behavior. This explains the characterization of the relative contribution of SAF and VF in dysmetabolism in pregnant women.[9] In the MUONW phenotype, the layer of subcutaneous adipose tissue is greater (while we were unable to discriminate between its superficial and deep layers, taking them into account together instead).

Increased subcutaneous adipose tissue would cause the visceral fat to increase its triglyceride accumulation function, causing a greater metabolic dysregulation, detectable by applying the proposed AADI.

AADI values in the different groups studied, characterized by notable differences between the phenotypes MHNW and MHONW, and between MHONW and MUONW, confirm the common characteristics that identify metabolically unhealthy obesity with MetS in the determination of the MUONW phenotype. This confirms what is posited in other studies that reveal an association of subcutaneous and visceral adipose tissue not just general adiposity—with various cardiometabolic risk factors.[30]

These results confirm the benefit of applying AADI in early pregnancy for normal-weight women, even when clinical manifestations of MetS have not been identified, which would allow for timely guidance regarding healthy behaviors.

The sensitivity demonstrated by the AADI diagnostic test with a high number of pregnant women correctly diagnosed with MetS, as well as the discriminant ability of this index for the MUONW phenotype in normal-weight women in early pregnancy, allows for diagnosis of the hidden risk of cardiometabolic disease based on ultrasound evaluation of SAF and VF. This demonstrates the robustness of the new index, which can be used in primary health care to reliably diagnose metabolic disorders at the start of pregnancy, with a practical value from the clinical perspective.

The principal limitation of this study is that the distinctive features of abdominal adiposity distribution were not studied, nor was its relationship with cardiometabolic risk factors in pregnant women according to their reproductive status.

The ultrasound measurement of SAF and VF and its later expression in the AADI together with the routine exam for normalweight women in the first trimester of pregnancy is simple, low cost and feasible, given the availability of US machines in primary health care in Cuba, as part of the nationwide Maternal-Child Care Program.

Unlike Panel III, here the direct measurement of abdominal fat is performed, which allows for reliable diagnosis of unhealthy obesity phenotypes like metabolically obese, normal-weight phenotype with increased risk of cardiovascular disease and MetS. In this way, complications may be avoided during pregnancy among women apparently at low obstetric risk.

### **CONCLUSIONS**

AADI is better than other traditional indicators at detecting the risk of metabolic obesity in early pregnancy in normal-weight women, facilitating early intervention in clinical practice to prevent or delay progression of cardiometabolic disease in these women.

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