The Lipid Accumulation Product for the Early Prediction of Gestational Insulin Resistance and Glucose Dysregulation

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Abstract

Background: Recent insights linking insulin resistance and lipid overaccumulation suggest a novel approach for the early identification of women who may soon experience glucose dysregulation. Among women without a history of gestational diabetes, we tested the association between the lipid accumulation product (LAP) obtained in early pregnancy and glucose dysregulation or insulin resistance in the second trimester.

Methods: A total of 180 white pregnant women of French-Canadian origin were included in this study. At 11–14 weeks' gestation, fasting insulin, glucose, C-peptide concentrations, and estimated insulin resistance (HOMA-IR) were obtained. The waist circumference (WC) and fasting triglycerides (TG) were measured to calculate LAP as $(WC_{[cm]} - 58) \times TG_{[mmol/L]}$. At 24–28 weeks' gestation, glucose was measured 2 hours after a 75-g oral glucose challenge and other fasting variables were repeated.

Results: Among the nulliparous women tested at the end of the second trimester, fasting insulin, C-peptide, insulin resistance (HOMA-IR index), fasting glucose, and 2-hour glucose progressively increased ($p \leq 0.002$) according to their first-trimester LAP tertiles. Similar results were observed in parous women except for the glucose variables. The first-trimester LAP tended to show a stronger correlation to the second-trimester HOMA-IR index ($r = 0.56$) than fasting triglyceride levels alone ($r = 0.40$) or waist circumference alone ($r = 0.44$) among nulliparous women. Similar associations were observed for parous women. Adjustment for body mass index weakened these associations, especially among parous women.

Conclusions: An increased value of LAP at the beginning of a pregnancy could be associated with an increased risk of insulin resistance or hyperglycemia later in gestation.

Introduction

GESTATIONAL INSULIN RESISTANCE AND hyperglycemia increase the risk for adverse maternal outcomes. It has been estimated that normal pregnancy is associated with a reduction of around 50% of insulin sensitivity combined with a 200% to 250% increase of insulin secretion, which helps maintain glucose homeostasis.¹ However, in some pregnancies characterized by very low insulin sensitivity (increased insulin resistance), glucose homeostasis may not be preserved throughout gestation, and glucose dysregulation occurs.^{2,3}

Pregestational obesity is an important risk factor for gestational insulin resistance and glucose dysregulation.^{4,5} In response to the emerging worldwide epidemic of obesity, which increasingly includes women of childbearing age,

gestational insulin resistance and glucose dysregulation could become significantly more frequent in the coming years.⁶ Moreover, not only are intermediate levels of maternal glucose and overweight both associated with adverse maternal and perinatal outcomes, but their impact would be even greater when combined.⁷ It follows that the burden of consequences associated with gestational glucose dysregulation goes beyond what can be estimated from gestational diabetes prevalence.

Programs to reduce the incidence of gestational diabetes and associated perturbations would benefit from simple screening tools allowing the early identification of the largest possible proportion of women who may soon experience a deterioration of their glucose regulation.⁸ Screening strategies for gestational diabetes are based partly on a woman's

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previous obstetric history.⁹ Although previous gestational diabetes expression is a strong independent predictor of repeated gestational glucose dysregulation, we cannot assume that a previous pregnancy without gestational diabetes protects women against problems of metabolic control. Parous women with a negative history for gestational diabetes, as well as nulliparous women, could still benefit from improved tools to assess their risk of insulin resistance and hyperglycemia.

An article from the Coronary Artery Risk Development in Young Adults (CARDIA) Study pointed out that an increased waist circumference or fasting triglycerides identified prior to conception was predictive of subsequent gestational diabetes.¹⁰ At about the same time, we reported, based on a sample of 144 pregnant women, that the "hypertriglyceridemic waist" phenotype identified in the first trimester could be a simple, readily accessible, and inexpensive early screening tool for gestational glucose intolerance.¹¹ The hypertriglyceridemic waist is a clinical marker of visceral obesity that is defined dichotomously as the simultaneous presence of abdominal obesity and hypertriglyceridemia.¹² However, its dependence on predefined thresholds for waist circumference and triglyceride concentration poses several problems. For example, the consequences of a continuous process, such as obesity or its related metabolic variables, cannot be adequately described by using a dichotomous risk marker. Indeed, binary variables inevitably lead to a loss of information.¹³ In addition, thresholds for waist circumference or triglycerides chosen in one population may not be suitable in another and may even be different for subgroups within the same population. It follows that the search for an early screening tool to predict gestational glucose dysregulation should explore the use of a continuous rather than a dichotomous marker.

The continuous lipid accumulation product (LAP), an index of central lipid accumulation, is computed by multiplying a sex-specific estimate of waist enlargement by the fasting triglyceride concentration; in women, $LAP = (WC_{[cm]} - 58) \times TG_{[mmol/L]}$.¹⁴ An increased LAP value is associated with a variety of prevalent cardiovascular risk factors¹⁴ and metabolic conditions such as prevalent diabetes,¹⁵ incident diabetes,¹⁶ the homeostasis model assessment of insulin resistance (HOMA-IR), an index used for the prediction of insulin resistance,^{17–19} and hepatic steatosis.²⁰ Considering that the LAP has been a successful risk marker in young adult populations, it could be a reliable marker of metabolic perturbations among pregnant women.

The aim of the present study was therefore to test the association between the LAP measured in the first trimester of pregnancy and the expression of disturbed glucose metabolism and insulin resistance later in pregnancy among women without a personal history of gestational diabetes.

Material and methods

Study design

This prospective cohort study comprised a sample of 180 white women of French-Canadian origin with a singleton pregnancy recruited at the beginning of their routine prenatal care at the Chicoutimi Hospital. Approximately 1500 deliveries take place each year at the Chicoutimi Hospital, an urban public hospital serving a population of over 160,000 inhabitants. At the time of this study, the Chicoutimi Hospital used the World Health Organization (WHO) criteria (a fasting

plasma glucose ≥ 7.0 mmol/L or ≥ 7.8 mmol/L 2 hours following the glucose challenge)²¹ for the diagnosis of gestational diabetes, which included a 75-g oral glucose tolerance test for all pregnant women. All women were sequentially recruited during their first visit, between October 2006 and December 2010. Women over 40 years old, those with type 1 or type 2 diabetes or other disorders known to affect glucose metabolism prior to pregnancy (including polycystic ovary syndrome), as well as those with a positive history of alcohol or drug abuse during the current pregnancy were excluded. Women with a prior personal history of gestational diabetes were also excluded since they were presumed to be at high risk for insulin resistance and hyperglycemia. The gestational age was calculated from the date of the last menstrual period and was thereafter corrected, as required, based on ultrasound data, if available. The drop-out rate before the 24–28 weeks' gestation visit was 5.2%. Written informed consent was obtained from all participants, and all clinical data were de-identified. The Chicoutimi Hospital Ethics Committee approved this project in accordance with the Declaration of Helsinki on April 25, 2006 (reference number 2005-034).

Measurements

A research nurse made all anthropometric measurements. Waist circumference at 11–14 weeks' gestation was measured at the midpoint between the iliac crest and last rib margin, after removing any clothing from this area, while the woman was in a standing position after normal expiration. The body mass index (BMI) was calculated as kilograms per square meter from the height and weight measured at the time of the first-trimester blood sample collection. Blood samples were obtained from the antecubital vein after a 12-hour overnight fast in the first trimester of pregnancy (11–14 weeks) and at the end of the second trimester (24–28 weeks). Following centrifugation, plasma glucose concentrations were measured by the glucose oxidase method and serum total triglyceride concentrations using enzymatic hydrolysis, on a CX7 Analyzer (Beckman Instruments, Fullerton, CA). The LAP index was calculated as follows¹⁴: $LAP = [waist (cm) - 58] \times \text{fasting triglyceride concentration (mmol/L)}$.

A radioimmunoassay method was used for insulin level quantification. C-peptide levels were measured using a commercially available ELISA kit (ALPCO Diagnostics, Salem, NH). The general coefficients of variation (CV) for insulin, triglyceride, and glucose, as measured by the Chicoutimi Hospital clinical laboratory, were 10.20%, 3.50%, and 3.74%, respectively. C-peptides levels were measured at the ECOGENE-21 research laboratory. The CV obtained among the pregnant women sample was 4.13%. At 24–28 weeks' gestation, plasma glucose concentrations were also measured 2 hours after a 75-g oral glucose challenge. Insulin resistance was estimated by HOMA-IR using the following formula¹⁷: $HOMA-IR = \text{fasting glucose (mmol/L)} \times \text{fasting insulin (mU/L)} / 22.5$.

Statistics

Group differences for continuous variables were compared with a Student's unpaired two-tailed *t*-test or an analysis of variance (ANOVA) followed by the Bonferroni *post hoc* test. The Pearson correlation coefficient was computed to quantify the linear association between the HOMA-IR index measured at the end of the second trimester and first-trimester LAP,

triglyceride levels, or waist circumference. The Hotelling's test was used to compare the correlation coefficients. The p values were two-sided. We considered results significant if $p < 0.05$. Analyses were performed with the SPSS package (release 20.0, SPSS, Chicago, IL).

Results

As shown in Table 1, 88 of the 180 women included in our study were parous. Among them, 64 (72.7%) had delivered once, 22 (25.0%) twice, and 2 (2.3%) three times. Maternal age was the only first-trimester variable significantly different between the parous and nulliparous groups ($p < 0.001$). Previous pregnancy did not appear to be associated with a significant increase in the LAP index measured in early pregnancy. No significant difference was found between the two groups for fasting glucose, 2-hour glucose, fasting insulin, C-peptide, or the HOMA-IR index measured at the end of the second trimester (not shown).

Fifteen nulliparous women and 17 parous women fulfilled gestational diabetes diagnosis criteria according to the WHO; however, with more stringent criteria, such as those of the International Association of Diabetes and Pregnancy Study Group, our sample included eight nulliparous women and five parous women with gestational diabetes. This prevalence was not significantly different between nulliparous and parous women ($p = 0.6$). Only in the nulliparous subsample were the first-trimester continuous values of BMI, triglycerides, insulin, HOMA-IR, and LAP associated with gestational diabetes, diagnosed according to the WHO criteria (not shown). However, considering the small number of women with gestational diabetes in both groups, the statistical power did not allow us to perform analyses of gestational diabetes according to categorical LAP tertiles.

Among the nulliparous women, fasting insulin, C-peptide levels, HOMA-IR index, fasting glucose, and 2-hour glucose measured at the end of the second trimester progressively

increased ($p \leq 0.002$) across the first-trimester LAP tertiles. Similar results were observed in parous women without a prior history of gestational diabetes except for glucose levels. Whereas their first-trimester LAP tertiles tended to be associated with a slight increase in 2-hour glucose concentrations ($p = 0.095$), no association was observed between their LAP tertiles and fasting glucose. All results obtained among nulliparous women remained similar when controlled for maternal age, BMI, and fasting glucose at first trimester. However, in parous women, results became nonsignificant after including the first-trimester BMI as a covariate (Table 2). Half of the women (90/180) were smokers before their pregnancy, 16% (29/180) still smoked during their pregnancy, and 42% (76/180) had a family history of type 2 diabetes. These proportions did not differ significantly between the tertiles (not shown).

The first-trimester LAP as a continuous variable was correlated with insulin resistance (as HOMA-IR; $p < 0.001$) measured at the end of the second trimester after adjustment for maternal age and first-trimester fasting glucose. The first-trimester LAP appeared to be a stronger correlate of the HOMA-IR index than fasting triglyceride levels alone for both nulliparous and parous women. However, the difference between the two correlation coefficients reached significance only among parous women ($p = 0.15$ and $p = 0.03$ in nulliparous and parous women, respectively). The correlation between HOMA-IR and LAP also tended to be stronger than the one observed between HOMA-IR and waist circumference, but only in nulliparous women. The same trend was observed after including BMI as a covariate. The correlation between HOMA-IR and LAP tended to be higher than the one observed between HOMA-IR and waist circumference also among parous women (Table 3). It is noteworthy that the correlation between fasting glucose at first-trimester and second-trimester HOMA-IR was comparable to the one observed with triglyceride levels alone and waist circumference among nulliparous women ($r = 0.44$; $p < 0.001$). However, the correlation between fasting glucose and HOMA-IR was not

TABLE 1. WOMEN'S CHARACTERISTICS AT THE FIRST TRIMESTER OF PREGNANCY^a

	Nulliparous women	Parous women	p	p ^b
<i>n</i>	92	88		
Age, years	27.4 ± 0.4	29.7 ± 0.4	< 0.001	—
Waist girth, cm	86.7 ± 1.3	89.2 ± 1.2	0.16	0.26
Height, m	1.63 ± 0.01	1.64 ± 0.01	0.66	0.97
Weight, kg	66.7 ± 1.5	66.8 ± 1.4	0.95	0.90
BMI, kg/m ²	24.9 ± 0.5	24.7 ± 0.5	0.76	0.70
Triglycerides, mmol/L ^c	1.02 ± 0.05	1.03 ± 0.05	0.91	0.47
Glucose, mmol/L	4.45 ± 0.04	4.40 ± 0.03	0.38	0.13
Insulin, mU/L ^{c,d}	5.92 ± 0.36	5.49 ± 0.43	0.34	0.49
HOMA-IR index ^{c,d}	1.16 ± 0.08	1.07 ± 0.08	0.32	0.40
C-peptides, pmol/L ^e	262.0 ± 12.6	274.2 ± 13.4	0.51	0.52
LAP ^c	27.06 ± 2.49	30.22 ± 2.34	0.24	0.16
Weight gain, % ^f	10.1 ± 0.4	9.8 ± 0.5	0.61	0.97

^aValues are mean ± SE. First trimester is equal to 11–14 weeks of gestation.

^bAge-adjusted p value.

^cGeometric means and p value obtained after log₁₀ transformation.

^d $n = 177$.

^e $n = 114$.

^fBetween the first and the second trimesters.

BMI, body mass index; HOMA-IR, estimated insulin resistance; LAP, lipid accumulation product.

TABLE 2. WOMEN'S CHARACTERISTICS AT THE END OF THE SECOND TRIMESTER OF PREGNANCY ACCORDING TO FIRST TRIMESTER LIPID ACCUMULATION PRODUCT TERTILES^a

	<i>Tertile 1 [2.0–22.4]</i>	<i>Tertile 2 [22.5–36.4]</i>	<i>Tertile 3 [36.5–150.1]</i>	<i>p</i>	<i>p^b</i>	<i>p^c</i>
Nulliparous women						
<i>n</i>	33	29	30			
Glucose, mmol/L	4.16±0.06	4.35±0.06	4.54±0.08 ^d	<0.001	0.001	0.001
2-h glucose, mmol/L	6.18±0.18	6.47±0.25	7.23±0.20 ^{d,e}	0.002	0.003	0.010
Insulin, mU/L ^{f,g}	5.46±0.49	8.09±1.09 ^d	11.00±1.17 ^{d,e}	<0.001	<0.001	0.002
HOMA-IR ^{f,g}	1.00±0.10	1.56±0.22 ^d	2.18±0.22 ^{d,e}	<0.001	<0.001	<0.001
C-peptides, pmol/L ^h	279.0±22.9	351.5±24.9	451.0±29.3 ^{d,e}	<0.001	<0.001	0.007
Parous women without a gestational diabetes personal history						
<i>n</i>	27	31	30			
Glucose, mmol/L	4.40±0.09	4.28±0.06	4.39±0.07	0.42	0.20	0.19
2-h glucose, mmol/L	6.37±0.25	7.02±0.21 ^d	6.62±0.17	0.095	0.094	0.096
Insulin, mU/L ^{f,i}	5.78±0.44	7.20±0.82	12.14±2.37 ^{d,e}	<0.001	<0.001	0.061
HOMA-IR ^{f,i}	1.12±0.09	1.36±0.18	2.36±0.41 ^{d,e}	<0.001	<0.001	0.12
C-peptides, pmol/L ^j	310.1±27.8	389.8±35.1	468.0±35.2 ^d	0.006	0.006	0.26

^aMean±SE.^bIncluding maternal age and fasting glucose in the first trimester as covariates.^cIncluding maternal age, fasting glucose, and BMI in the first trimester as covariates.^d*p*<0.05 as compared to Tertile 1.^e*p*<0.05 as compared to Tertile 2.^fGeometric means and *p* value obtained after log₁₀ transformation.^g*n*=89 (T1=32, T2=29, T3=28).^h*n*=55 (T1=22, T2=15, T3=18).ⁱ*n*=83 (T1=25, T2=28, T3=30).^j*n*=56 (T1=17, T2=18, T3=21).

significant among parous women (*r*=0.065; *p*=0.56) (not shown).

Discussion

Our study is the first to analyze the association between LAP and gestational insulin resistance and glucose dysregulation among finely-phenotyped women recruited early at the beginning of pregnancy. We have shown that LAP measured in the first trimester of pregnancy was associated with an increased gestational insulin resistance at the end of the second trimester. LAP was also associated with subsequent gestational hyperglycemia, most clearly among nulliparous women.

The present study is a continuation of the previous one.¹¹ We now benefit from a larger sample with an enhanced clinical evaluation, including more detailed measures of insulin resistance. Further, most of our additional participants

were nulliparous, which allowed us to perform analyses among women without a personal history of gestational diabetes. The results from the present study have extended our earlier report¹¹ primarily by introducing the use of a continuous risk marker (LAP) in place of a dichotomous marker (hypertriglyceridemic waist). Because LAP does not depend on thresholds previously defined in only one community, it can be used in other subpopulations distinguished by age, ancestral origins, or other characteristics. As a continuous variable, LAP also allows researchers to more easily identify the quantitative relationships that could be obscured by use of a categorical variable,¹³ and it could facilitate an improved understanding of the processes behind gestational glucose dysregulation and insulin resistance.

In modern societies characterized by an increasing prevalence of obesity, gestational insulin resistance occurs in parallel with enhanced maternal adipose tissue deposition prior to pregnancy, associated lipid accumulation, and related

TABLE 3. CORRELATIONS BETWEEN INSULIN RESISTANCE ESTIMATED AT THE END OF THE SECOND TRIMESTER AND FIRST-TRIMESTER LIPID ACCUMULATION PRODUCT, TRIGLYCERIDE LEVELS, OR WAIST CIRCUMFERENCE

Independent variables (measured at first trimester)	Outcome variable: second-trimester HOMA-IR ^a			
	Adjusted for maternal age and fasting glucose in first trimester		Adjusted for maternal age, fasting glucose and BMI in first trimester	
	Nulliparous women (<i>n</i> =89)	Parous women (<i>n</i> =83)	Nulliparous women (<i>n</i> =89)	Parous women (<i>n</i> =83)
LAP index	<i>r</i> =0.56, <i>p</i> <0.001	<i>r</i> =0.59, <i>p</i> <0.001	<i>r</i> =0.42, <i>p</i> <0.001	<i>r</i> =0.33, <i>p</i> =0.003
Triglyceride	<i>r</i> =0.40, <i>p</i> <0.001	<i>r</i> =0.34, <i>p</i> =0.002	<i>r</i> =0.31, <i>p</i> =0.004	<i>r</i> =0.26, <i>p</i> =0.018
Waist circumference	<i>r</i> =0.44, <i>p</i> <0.001	<i>r</i> =0.57, <i>p</i> <0.001	<i>r</i> =0.20, <i>p</i> =0.06	<i>r</i> =0.15, <i>p</i> =0.17

^aThe correlation coefficients (*r*) and *p* values were calculated after log₁₀ transformation of LAP, triglyceride levels, and HOMA-IR.

features that characterize a prodiabetogenic environment for both the mother and offspring.²² Among parous women, adipose tissue is enlarged preferentially in the visceral compartment, independent of overall excess total body fat accumulation.²³ Considering the deleterious short- and long-term consequences, the gestational accumulation of lipids and its associated insulin resistance may require recognition early in pregnancy, even in nonobese women, to facilitate preventive strategies. However, the expansion of visceral adipose tissue cannot be assessed accurately by simple and accessible markers such as BMI or even waist circumference. The characterization of visceral fat accumulation by imaging and insulin resistance by clamp methods is often expensive and may be especially challenging for pregnant women. The LAP has been suggested as an inexpensive and highly accessible index developed to measure the continuous relation between adiposity and its related cardiometabolic consequences.^{14,15} It has notably been associated with prevalent and incident diabetes^{15,16} as well as insulin resistance in women with polycystic ovary syndrome.¹⁸ Not only has LAP been shown to be a useful marker of glucose dysregulation among young women, but it is also a predictor of mortality among older women.²⁴ In this context, the LAP is an attractive new candidate marker for use in maternity care. Our results show that LAP may be a good predictor of insulin sensitivity and glucose dysregulation among pregnant women, even after adjustment for known covariates. The first-trimester LAP could therefore be used for early identification of women at risk of perturbed glucose metabolism before hyperglycemia or gestational diabetes are recognized later in their pregnancy. We can go further and imagine that increased LAP during pregnancy could also identify women most likely to develop type 2 diabetes in the postpartum period, even among those with glucose perturbation below the diagnostic thresholds for gestational diabetes diagnosis.

Several reports have indicated that maternal obesity before or at the beginning of pregnancy is a risk factor for gestational diabetes.⁵ High levels of circulating triglycerides also have been associated with maternal and fetal complications of pregnancy.^{25,26} Our study suggests that the combination of both central obesity and circulating triglycerides in a single indicator could serve to predict several medical outcomes that merit clinical attention.

Interestingly, whereas the first-trimester LAP was significantly associated with markers of insulin resistance at the end of the second trimester in both nulliparous and parous women, the association of LAP with glucose variables was not significant among parous women. Moreover, the first-trimester fasting glucose level did not appear to be a good correlate of the second-trimester HOMA-IR index in parous women. The factors that protected these parous women from gestational diabetes in their previous pregnancies—for example, the presence of robust pancreatic beta cells capable of responding to increased insulin resistance—could continue to influence the association between the LAP, glucose levels, and insulin sensitivity in our observational cohort. Our study design intentionally excluded parous women who previously experienced gestational diabetes; this could partly explain why there was no significant difference of BMI or LAP between both groups. Further, this strategy reduced the number of parous women likely to have beta-cell dysfunction (diminished insulin production). For this reason, our parous

subgroup could be more capable of maintaining glucose homeostasis than the nulliparous subgroup. However, interestingly, the proportion of gestational diabetes during the current pregnancy was the same among nulliparous and parous women, suggesting that other process may be involved. In addition, it has been shown that a redistribution of adipose tissue, characterized by a decrease in hip and thigh circumferences and an accumulation of abdominal fat, independent of BMI tends to be observed over successive pregnancies.²⁷ This observation suggests that insulin resistance in these women could be independent of BMI. This could partly explain why results become nonsignificant in parous women but not in nulliparous women after including the first-trimester BMI as a covariate, even though the BMI mean values were not significantly different between the two groups; it could also explain why the range was not wider among parous women.

Few women included in our study fulfilled the gestational diabetes criteria. Most had only modest glucose dysregulation. Rather than a possible weakness, we believe that this situation gives our results a particular clinical interest. Although more studies are needed to clearly assess the risk associated with intermediate maternal hyperglycemia and insulin resistance, especially in absence of gestational diabetes, it has been clearly shown that women without gestational diabetes who had only mildly elevated glucose concentrations during pregnancy would benefit from better (and early) glucose metabolism monitoring during pregnancy.²⁸ Our results suggest an easily accessible way to estimate the individual risk in order to improve close monitoring. Since our study design enabled us to detect a significant association with only mildly elevated glucose concentrations and insulin resistance, we hypothesize that these results should at the very least remain unchanged with the most severe glucose dysregulation. However, our results should be replicated in larger samples and more diversified populations, including women with more severe deteriorations of glucose and insulin metabolism.

Conclusion

The LAP obtained in the first trimester appears to be a good predictor of insulin resistance among pregnant women with no personal history of gestational diabetes. Our confidence in these results leads us to suggest that LAP might one day be used at a first prenatal visit or possibly prior to conception for the early identification of high-risk mothers. But we are still far from implementing such changes without further studies of women from more varied populations. Our results suggest that LAP might be a particularly attractive tool in order to develop early, accessible means to improve preventive strategies. Such an outcome would prove timely in the context of the increasing prevalence of obesity.

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Author Disclosure Statement

No competing financial interest exist.

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