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Case Series

Gestational diabetes and endothelial function: impact of gestational insulin resistance on reactive hyperhemia index

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ABSTRACT

Our aim was to characterize endothelial function in gestational diabetes by evaluating the reactive hyperemia index (RHI, LnRHI). A prospective, descriptive and comparative study was conducted on a population of pregnant women aged over 20 and under 36, located in the gestational age group 24-38th week of amenorrhea. They were divided into two groups. Group 1 (G1): group of pregnancies without diabetes, consists of pregnant women with no risk factor for gestational diabetes and with normal fasting blood glucose. Group 2 (G2): group of pregnancies with diabetes, includes pregnancies whose oral glucose tolerance tests (OGTT) came back positive. Anthropo-physiological parameters (age, weight, height, blood pressure (PA) and biochemical parameters (glycemia, insulinemia, HOMA-IR, cholesterol, triglycerides) were measured. RHI and LnRHI were determined at Endopat 2000. The two groups were matched for age, weight, heart rate (HR) and blood pressure (BP). Levels of glucose (G1:0.76±0.11; G2:1.11±0.11; p<0.0001), insulin (G1:7.67±4.35; G2:22.9±3.75; p<0.0001), HOMA-IR (G1:1.51±0.97; G2:6.29±1.23; p<0.0001), total cholesterol (G1:1±0.81; G2:2.49±0.74; p=0.002), HDL cholesterol (G1:0.45±0.23; G2: 0.8±0.19; p=0.004, LDL cholesterol (G1:0.42±0.54; G2:1.39±0.6; p=0.004), triglycerides (G1:0.65±0.49; G2:1.48±0.27; p=0.0018), were significantly higher in the diabetic group. Both RHI and LnRHI were negatively correlated with HOMA-IR (respectively, r=-0.8931, p<0.0001; r=-0.8938; p<0.0001). HOMA-IR index was independently associated with levels of RHI and LnRHI (respectively r^2=0.797; p<0.0001); (r^2=0.804; p<0.0001)). Thus, gestational insulin resistance would be associated with a change in endothelial function such as a decrease in endothelium-dependent vasodilatation reflecting endothelial dysfunction, hence an increase in cardiovascular risk.

Keywords: Gestational diabetes, Insulin resistance, Reactive hyperhemia index, Endothelial dysfunction

INTRODUCTION

Gestational diabetes is a carbohydrate tolerance disorder leading to hyperglycaemia of variable severity, beginning or diagnosed for the first time during pregnancy.[1]

It is associated with an increase in maternal and fetal morbidity and mortality during pregnancy but also in the longer term.

Therefore, gestational diabetes is a real public health problem.

It is the result of an inability of the pregnant woman to increase her insulin secretion in response to insulin resistance induced by the metabolic adaptations of pregnancy. To maintain normotensive homeostasis, the orchestrated collaboration of the different vasodilator systems is necessary in the systemic and local hemodynamic adaptations during pregnancy. Among these systems, the vascular endothelium is described as an independent endocrine organ that produces factors involved in processes, such as hemostasis, angiogenesis, vasomotor and inflammatory responses.[2,3]

In Africa, particularly in Senegal, there are very few studies on the mechanisms involved in the occurrence of gestational diabetes and its complications. Based on this observation, we initiated this work with the aim of exploring endothelial function during gestational diabetes in a Senegalese population in the last trimester of pregnancy.

CASE SERIES

Subjects

A prospective, descriptive and comparative study on a population of 14 pregnant women divided into two groups. Group 1 (G1), representing the group of pregnancies without diabetes, is made up of pregnant women regularly followed in prenatal consultation, without risk factors for gestational diabetes and with normal fasting blood sugar. Group 2 (G2), being the group of pregnancies with diabetes, includes pregnancies regularly followed in prenatal consultation whose diagnostic test for gestational diabetes came back positive (high fasting blood sugar and/or oral induced hyperglycemia test (OGTT) came back positive). These women were over 20 years old and under 36 years old, were in the same gestational age group 24-38th week of amenorrhea and suffered from no other progressive chronic disease except diabetes discovered during pregnancy.

Experimental protocol

The protocol was performed according to the statements of Helsinki and was approved by the ethics Committee of the University (Ref:0051/2015/CER/UCAD). Participants were informed about the procedure and the purpose of the study and have given their written informed consent. The study was conducted at the University Cheikh Anta Diop of Dakar-Senegal-West Africa. It was performed at the Laboratory of Physiology and Functional Explorations of the Faculty of Medicine and at the Laboratory of Biochemistry and Molecular Biology, Faculty of Medecine, Pharmacy and Odontology of Cheikh Anta Diop University.

Anthropometrical and physiological parameters

Determination: For each patient we performed were (1) an interrogation in search of risk factors and medical, gynecological-obstetrical and surgical history, (2) a complete clinical examination including constants, anthropometric and physiological data (age, height, weight, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (PAD), (3) the weight was taken by a Terraillon brand scale, (4) height was measured with a measuring rod graduated in centimeters, (5) Blood pressure and heart rate were assessed using a sphygmomanometer fitted with a Braun Bp6000 frequency meter.

For each patient we have developed an examination sheet where the data of the interrogation and the clinical examination are collected.

Characteristics: The values of the measured anthropometric and physiological constants are summarized in Table 1.

Table 1: Average of anthropometric and physiological constants.

Anthropometric and physiological parameters	Control group	Gestational diabetes group	P value
Age (years)	30.5±5.7	32.1±5.3	0.296
weight (kg)	71±1.2	74.3±1.6	0.344
Height (m)	1.69±0.06	1.61±0.05	0.020
SBP (mm Hg)	108.9±9.1	118.4±10.8	0.057
DBP (mm Hg)	70±6.3	69.3±6.1	0.419
MBP (mm Hg)	83±7.07	75±2.9	0.249
HR (bttm)	88.1±6.5	92.8±8.2	0.145

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean arterial pressure; HR: Heart rate; P value (p): significance level <0.05.

The anthropo-physiological parameters, apart from height, did not reveal any significant difference between the two groups. It should be noted that the average blood pressure, weight and heart rate were normal in both groups. Thus, the two groups in our study population were matched according to age (G1:30.5±5.7 years; G2:32.1±5.3 years; p=0.296), weight (G1:71±1.2 kg; G2:74.3±1.6 kg; p=0.344), blood pressure (BP) (Systolic BP: [G1:108.9±9.1 mmHg; G2:118.4±10.8 mmHg; p=0.057]; Diastolic BP: [G1:70±6.3 mmHg; G2:69.3±6.1 mmHg; p=0.419]; Mean BP: [G1:88.1±6.5 mmHg; G2:75±2.9 mmHg; p=0.249] and heart rate (G1:88.1±6.5 bttm; G2:92.8±8.2 bttm; p=0.145) (Table 1).

Biochemical parameters

Determination: For the dosage of the biochemical parameters, a fasting venous sample was taken. Samples were taken from (1) gray fluorinated tubes (as an anticoagulant sodium fluoride and potassium oxalate) for measuring blood sugar, (2) dry tubes (without anticoagulant) to determine the other biochemical markers.

The automatic spectrometer (chemistry module LEc4000 of architect system ci4100) was used for the biochemical assays. We measured plasma glucose concentrations and serum insulin, triglycerides (TG), total cholesterol (Tchol), HDL cholesterol (high density lipoprotein cholesterol (HDLchol)). The LDL cholesterol (low density lipoprotein cholesterol (LDLchol)) levels were obtained by calculation using the Friedwald formula: LDLChol = TChol-HDLChol-TG/5.

The HOMA-IR (Homeostasis Model assessment of insulin resistance) index was calculated using the equation: HOMA-IR = insulin (µIU/ml) × glucose (mg/dl).

Biochemical characteristics: Table 2 highlights the biological markers explored in our study.

Levels of glucose (G1:0.76±0.11; G2:1.11±0.11; p<0.0001), insulin (G1:7.67±4.35; G2:22.9±3.75; p<0.0001), HOMA-IR (G1:1.51±0.97; G2:6.29±1.23; p<0.0001), Total cholesterol (G1:1±0.81; G2:2.49±0.74; p=0.002), HDLcholesterol (G1:0.45±0.23; G2:0.8±0.19; p=0.004, LDLcholesterol (G1:0.42±0.54; G2:1.39±0.6; p=0.004), triglycerides (G1:0.65±0.49; G2:1.48±0.27; p=0.0018) were significantly higher in the diabetic group. Then, glucose, insulin, HOMA index and lipid variables show that the abnormalities predominate significantly in the gestational diabetes group (Table 2).

Table 2: Mean of biological variables.

Biological variables	Control group	Gestational diabetes group	P value
Glucose (g/l)	0 .76±0.11	1.11±0.11	<0.0001
Insuline (µU/ml)	7.67±4.35	22.9±3.75	<0.0001
HOMA-IR index	1.51±0.97	6.29±1.23	<0.0001
Cholestérol total (g/l)	1±0.81	2.49±0.74	0.002
Cholestérol HDL (g/l)	0.45±0.23	0.8±0.19	0.004
Cholestérol LDL (g/l)	0.42±0.54	1.39±0.6	0.004
Triglycérides (g/l)	0.65±0.49	1.48±0.27	0.0018

HOMA-IR index: index of Homeostasis Model assessment of insulin resistance; P value (p): significance level <0.05.

Exploration of endothelial function

Equipment: As part of our study, we used the Endopat 2000: recording version 3.5.4; analysis version 3.5.4 (2.0). It is widely recognized as the standard method for the assessment of endothelial function. This is a device that measures peripheral arterial tone for the non-invasive assessment of endothelial function.

Principle of operation, conditions and conduct of the examination: Its operating principle is based on the non-invasive measurement of peripheral arterial tone using single-use biosensors placed on the index fingers of both hands.

Before proceeding with the measurement, we first ensured that the patient was fasting for at least 4 hours before the session and had abstained for at least 8 hours from consuming caffeine, tobacco, vitamins or medication which could temporarily modify the vascular tone. To minimize the risk of vascular fluctuations, the study was conducted in a quiet, low-light environment at controlled room temperature.

For the smooth running of the examination and to obtain reliable results, the subject is lying in the supine position during the time of the measurement.

The examination involves measuring endothelium-mediated tone changes in the vascular pathways. These arterial tone changes are elicited by creating a hyperemic response induced by a standard 5-minute brachial artery occlusion performed with an inflatable cuff.

The inflation cuff is positioned on the non-dominant arm at the lower part near the elbow crease. The Endopath biosensors are then placed on the index fingers of both arms after checking the size of the nails and the condition of the skin. The test lasts 15 minutes (min): after recording the baseline for 5 min, a vascular occlusion of 5 min is performed by inflation of the cuff then after deflation the recording is continued for 5 min until the return to the line basic. Contralateral arm measurements are used to monitor concurrent non-endothelium-dependent changes in vasculature.

Results and disorders targeted: The automatically calculated result gives the index of endothelial function called: reactive hyperemia index (RHI). This index reflects the endothelium-dependent vasodilatation capacities of the subject's blood vessels and thus makes it possible to detect endothelial dysfunction at the subclinical stage.

A normal post-occlusive response should be manifested by an endothelium-dependent dilation which results in an increase in the amplitude of the PAT signal. A post-occlusion/pre-occlusion ratio is calculated by the Endopat software.

The normal values of the hyperaemia reactivity index (RHI) and its logarithm (LnRHI) are respectively “1.67 to 2” and “0.51 to 0.70”. An RHI value of less than 1.67 can therefore be considered as evidence of vascular dysfunction. In other words: (1) the endoScore™ is normal if RHI>1.67 or LnRHI>0.51, (2) the endoScore™ is abnormal if RHI≤1.67 or LnRHI≤0.51.[4]

Characteristics of endothelial factors in study population: The endothelial factors measured (reactive hyperemia index (RHI) and its logarithm) show the presence or absence of endothelial dysfunction.

The characteristics of endothelial dysfunction parameters are expressed in Figure 1.

Compared to the gestational diabetes group, the reactive hyperemia indices (RHI and LnRHI) are on average higher in the normal pregnancy group (respectively: control: 1.52±0.1 GDM: 1.3±0.06; p<0.05; control: 0.4±0.06; GDM:0.28±0.03; p<0.05).

The distribution of endothelial abnormalities according to diabetic or non-diabetic status is shown in Table 3.

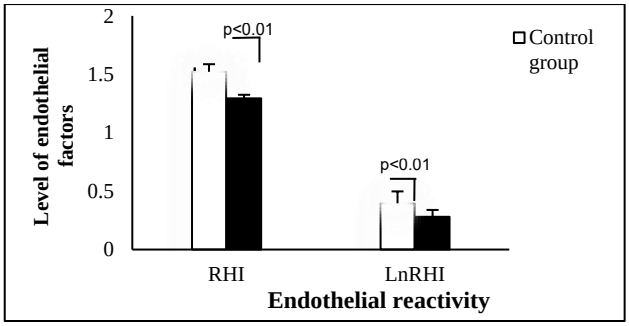

Figure 1: Comparison reactivity of endothelial factors (RHI, LnRHI) between two groups.

RHI: reactive hyperemia index; LnRHI: logarithm of reactive hyperemia index; Pvalue (p): significance level < 0.05; Control group: women with normal pregnancy; Gestational diabetic group: women with diabetic pregnancy.

Table 3: Distribution of endothelial abnormalities between the two groups.

	RHI				LnRHI			
	Normal		Abnormal		Normal		Abnormal	
	N	%	N	%	N	%	N	%
Normal pregnancies	3	43	4	57	3	43	4	57
Diabetic pregnancies	0	0	7	100	0	0	7	100

RHI: reactive hyperemia index; LnRHI: logarithm of reactive hyperemia index.

In the control group, we found that 4 of the 7 patients (57%) had lower than normal RHI and LnRHI values (confirmation of endothelial dysfunction). Concerning the diabetic group, all the patients (i.e. 100%) have abnormal RHI and LnRHI values.

It can be deduced that the decrease in RHI and its logarithm, indicating endothelial dysfunction, is more frequent in diabetic pregnancies compared to normal pregnancies (Table 3).

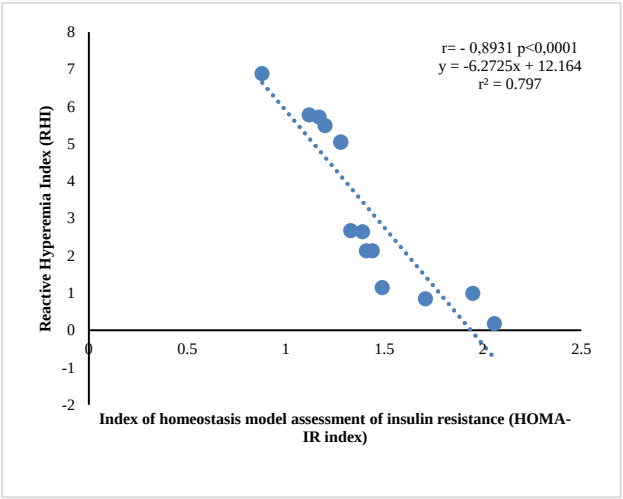

Figure 2: Link between RHI and HOMA-IR index

r: correlation coefficient; p: p value: significance level <0.05; r²: Determination of the coefficient of measurement of the predictive quality of the linear regression.

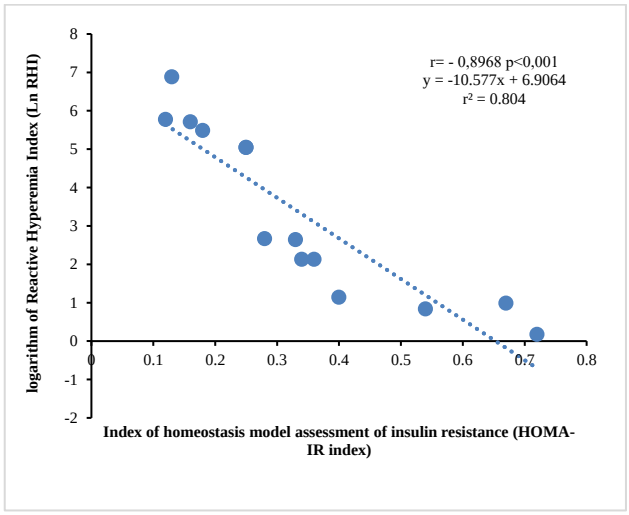

Figure 3: Link between LnRHI and HOMA-IR Index.

r: correlation coefficient, p : p value: significance level <0.05, r²: Determination of the coefficient of measurement of the predictive quality of the linear regression.

The links between endothelial factors and insulin-carbohydrate variables through the HOMA insulin resistance index, are revealed in Figures 2 and 3.

Univariate analyzes showed that RHI and LnRHI were negatively correlated with the HOMA-IR index (respectively, r=-0.8931, p<0.0001; r=-0.8938; p<0.0001). The determination of the linear regression revealed that the HOMA-IR index was independently

associated with the levels of RHI and LnRHI (respectively r^2=0.797; p<0.0001); (r^2=0.804; p<0.0001)); (Figures 2 and 3).

DISCUSSION

The anthropo-physiological and biochemical profile of our study population

Our study population consisted of pregnant women between the ages of 20 and 35. They were located in the gestational age group 24-35th week of amenorrhea. Apart from gestational diabetes, they had no other history of cardiovascular disease or risk factors.

The choice of such a population profile is explained by the fact that studies have shown that certain factors such as advanced age (>39 years), arterial hypertension, hypercholesterolemia, tobacco, pathologies renal and cardiovascular, affect vascular function.[5,6]

Therefore, to ensure that the effect on the vessels is exclusively due to gestational diabetes, we opted to exclude pregnant women presenting or having presented any cardiovascular risk that could modify endothelial function.

Additionally, studies have suggested that circulatory changes most often occur in the third trimester of pregnancy.[7-10] Based on this fact, we opted in our study to include only pregnancies with a gestational age greater than or equal to 24 weeks of amenorrhea.

Our results revealed that diabetic pregnancies were hyperglycemic, hyperinsulinaemic, insulin resistant with a high HOMA index and dyslipidemic with significantly increased total cholesterol and triglyceride levels. Our observations are in agreement with the data of certain authors who found that an index of HOMA-IR>2.4, expressed an underlying insulin resistance.[11,12] The latter, also called insulin insensitivity, will systematically lead to an increase in the level of circulating insulin. This is how several studies link hyperinsulinemia to insulin resistance, with the exception of insulin secretory deficiency.[13-15] This insulin resistance is also associated with dyslipidemia and the high cardiovascular risk usually found in arterial hypertension, obesity, hypertensive type 2 diabetes but also in gestational diabetes.[10,13,15-18]

The vascular endothelial profile

With regard to the vascular system, it has been proven that beyond the usual risk factors, the reactive hyperemia index as well as its logarithm (respectively RHI and LnRHI) are among the predictive factors of cardiovascular morbidity and mortality.[2,19] Hence the importance of exploring endothelial function by measuring these indices during gestational diabetes.

The evaluation of endothelial factors (RHI and LnRHI) within our study population revealed lower values in all pregnancies of the diabetic group. This reflects the presence of endothelial dysfunction which is generally expressed in the form of a deterioration in endothelium-dependent relaxation with a decrease in RHI.[2]

This index of endothelial dysfunction found in our entire population of diabetic pregnancies, could be one of the initiating factors of a whole series of cardiometabolic abnormalities leading to an alteration of the cardiovascular system. This corroborates the observations of certain previous studies which have shown that diabetes occurring during pregnancy seems to significantly increase the risk of occurrence of cardiovascular pathologies in women who have had a history of gestational diabetes.[16,18]

Our results also agree with those of several studies which have confirmed that gestational diabetes is associated with endothelial dysfunction.[2,20,21] It has also been proven that women with pregnancies complicated by gestational diabetes have impaired endothelial function. This endothelial dysfunction is thought to be linked to dysregulation of glucose metabolism.[22]

The link between insulin resistance and endothelial dysfunction

In our study, we found in the gestational diabetes population, a negative correlation between the HOMA insulin resistance index and the RHI as well as the LnRHI. This link between insulin resistance in the GDM and endothelial dysfunction has been amply established in diabetic pregnancies.[23,24]

In sum, our results suggest that endothelial dysfunction, determined by the decrease in RHI and LnRHI, provides an index of vascular status. This corroborates the results of several authors according to which endothelial dysfunction is an underlying manifestation in many vascular pathologies.[25,26] This affection of the vascular endothelium would be involved in the initiation and development of the atherosclerotic plaque at the origin of the first athero-thrombotic clinical manifestations.[27,28]

CONCLUSION

The effect of gestational diabetes on endothelial function was established by exploring two endothelial factors: RHI and LnRHI. This allowed us to show that gestational insulin resistance would be associated with a change in endothelial function such as deterioration of endothelium-dependent vasodilation, reflecting endothelial dysfunction. Thus, gestational diabetes turns out to be associated with the occurrence of various maternal complications, one of the main ones being the increase in cardiovascular risk. The measurement of the reactive hyperemia index and its logarithm would reflect vascular changes predictive of later cardiovascular complications.

However, increasing the size of our sample in our subsequent studies will increase the statistical power of our results.

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