Original Research Article

Insulin resistance and arterial stiffness: impact of gestational diabetes on pulse wave velocity

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ABSTRACT

Background: Gestational diabetes is an intolerance of glucose with the first appearance during the pregnancy. This hyperglycaemia status, because of the pre-existing insulin-resistance, constitute a favourable land of arterial stiffness. The aim of this study is to determine the impact of non obese gestational diabetes on arterial stiffness by measuring the pulse wave velocity (PWV).

Methods: We recruited 60 pregnant women aged from 20 to 35 years old. They were between twentieth four and thirtieth five weeks of gestational age. Subjects were divided into two groups: the first group (G1), considered as control group, included 25 normoglycemic pregnant subjects without any history of illness or risk factors of gestational diabetes; the second group (G2) included 35 women with Gestational Diabetes Mellitus (GDM). All pregnant women had not history of smoking, were not taking decoction or medicine, which could disturb pregnancy evolution. Anthropo-physiological and biochemical parameters studied, were: age, body mass index (BMI), blood pressure (BP), triglyceride, cholesterol and HOMA-IR index. The PWV between finger and toe (PWVft) was measured by pOpmètre®.

Results: The two groups are matched by age (G1:28±4ans; G2:29±3ans) and BMI (G1:25.6±1.27; G2:26.9±1.3). Blood pressure (BP) values are in normal interval (systolic BP: [110-132mmHg]; diastolic BP: [63-87mmHg]; mean BP: [79-103mmHg]). Total cholesterol (G1:0.95±0.08;G2:2.4±0.7; p<0.0001), HDL cholesterol (G1:0.44±0.02; G2:0.76±0.2; p<0.0001, LDL cholesterol (G1:0.40±0.05; G2:1.3±0.5; p<0.0001), triglyceride (G1:0.57±0.45; G2:1.6±0.4;p<0.0001), HOMA.IR (G1:1.31±1.05; G2:7.4±1.07; p<0.01), PWVft (G1:5.99±1.23; G2:10.3±1.9; p<0.0001) are significantly higher in diabetic group. PWVft is positively correlate to HOMA-IR index, total cholesterol, LDL cholesterol and triglycerides (r=0.3348, p=0.032; r=0.5275, p<0.0001; r=0.4855,p<0.0001; r=0.5581, p<0.0001respectively).

Conclusions: Gestational diabetes might induce an increase of pulse wave velocity expressing increment of arterial stiffness. This last constitute an early underlying cardiovascular risk.

Keywords: Arterial stiffness, Gestational diabetes, Insulin resistance, Pulse wave velocity

INTRODUCTION

Gestational diabetes Mellitus (GDM) is defined as a glucose intolerance with the first appearance or the first recognition during pregnancy.[1] It is a frequent

complication of pregnancy. In the last decade, several studies suggested an upward tendency of the incidence of gestational diabetes. In the world, the global incidence is actually estimated from 1% to 14% according to the studied population and based on the choice and the moment of the gestational diabetes diagnosis.[2-5]

Pregnancy is associated with important changes concerning the whole of metabolism allowing growth of fetoplacental unit.[6,7] The variations on the cardiovascular, hemodynamic, hematologic, hormonal and hepatic level may have a potential interaction with the physiopathology of gestational diabetes. Amongst the modifications that can occur on the normal process of pregnancy, there is the arterial vasodilation leading to the increase in 50% of cardiac output by increase in the heart rate and the stroke volume. The blood volume increase in 40% under hormonal influence.[8] Venous and arteriolar system control the whole of these changes making a stable blood pressure.[9]

Pregnancy leads also, the secretion of several steroid and peptide hormones whose the influence on vascular system is discussed. Beyond increasing of blood volume, pregnancy make some change of hemostasis.[9]

Pregnancy associated to diabetes seems significantly increase the risk of developing cardiovascular deseases in women with gestational diabetes background.[10,11] This association is characterized by biological changes whose an impairment on glucidic, lipidic and renal level. It would be responsible for inflammation and endothelial dysfunction.[12]

This endothelial dysfunction would promote arterial stiffness in type II diabetic subjects.[13] Arterial stiffness or arteriosclerosis depend on several factors such as the structural proprieties of arterial wall : it is an arterial accelerated ageing.[14]

In sub-Saharan Africa, there are very few search relating to gestational diabetes. A better knowledge of mechanism involved in the occurrence of vascular events during gestational diabetes, will provide an effective means of preventing and a better care.

That's how, the aim of the present study is to assess in black african people, the impact of gestational diabetes on the vessel wall quality or stiffness by measuring the pulse wave velocity finger-toe (PWVft) with the pOpmetre device.

METHODS

Subjects

We've processed through a prospective, descriptive and cross-sectional study of pregnant women. 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.

The present study included 60 pregnant women aged over 20 years and under the age of 36 years. They have no chronic pathology in progress except diabetes occured during pregnancy. With regards to their gynecological status, they were between twentieth four and thirtieth five weeks of gestational beam.

Determination of anthropometrical and physiological variables

For the conduct of the study, we used the following material:

- An height gauge to measure in centimetre the height of the subjects,
- A scales (Terraillon) to assess the weight in kilogram,
- A sphygmomanometer with a frequency meter (Braun BP6000) to determine the blood pressure and the heart rate,
- Record cards on which we collected the outcomes of history and physical examination.

The body mass index (BMI) also called Quetelet index, was determined on the basis of weight (W) and height (H) using the Quetelet formula : $BMI = W (kg)/H^2(m^2)$.[15]

In a paraclinical view, samples were done after an overnight fast (around 12 fasting hours). Device using for vascular exploration is the pOpmètre ® 300 ENR-DT-07 V2ß 22032016 designed, tested and approved according to international standards NF EN60601-1(éd.3) and EN00601-12:2007.

The pOpmètre® 300 S is a non-invasive medical device destined for measuring off pulse wave velocity (PWV). The main function of this system is to measure the time separated the pulse wave velocity between finger and toe. The machine is connected to the patient by photodiode sensors (photoplethysmographic).

Conditions for the used are those of the recommendations of the European Society of cardiology (ESC) and hypertension (ESH) concerning the measure of blood pressure and arterial stifness.The measure of arterial stiffness are realized:

- In a quiet room with a stabilized temperature (between 22 to 23°C),

- In patient in a supine position, at rest for 5 to 10 minutes without speaking or sleeping,
- At least 2 hours after following, a meal, a coffee-making or cigarettes,
- For a period longer than a breath cycle (5 to 6 seconds).

The sensors are positioned on the index finger and the second toe on the same side, the pulp is contacted with the black side of the sensor. The subject is in supine position, her arms at her side. For each women included in this study, we have proceeded to:

- An interrogation searching medical, gyneco-obstetrical and surgical background.
- A full clinical examination including the constant-taking, the collection of anthropometrical and physiological data (age, weight, height, body mass index (BMI), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP))
- A fasting venous sample for the determination of biochemical parameters.
- A measurement of pulse wave velocity between finger and toe (PWVft) using pOpmètre®. The target disorder is arterial stiffness defined by the measured value of pulse wave velocity finger-toe (PWVft) relative to the predictive normal value.

The diagnostic criteria of arterial stiffness are defined age-depending in accordance with the reference values established by Reference Values for Arterial Stiffness' Collaboration.[16]

Our pregnant women were divided into 2 groups according to their diabetic status (G1: controls and G2: Gestational Diabetes). Data obtained were compared between two groups.

Determination of biochemical parameters

Biochemical parameters were analysed by using automatic spectrometer (chemistry module LEc4000 of architect system ci4100). We determined plasma glucose concentrations and serum levels of insulinemia, triglyceride (TG), total cholesterol (Tchol), high density lipoprotein cholesterol (HDLchol). Low Density Lipoprotein cholesterol (LDLchol) concentrations were calculated by *Friedwald formula*:

$$LDLChol = TChol-HDLChol-TG/5.$$

Statistical analysis

Samples were analysed using GraphPad Prism version 5.2. Data were expressed as mean ±standard deviation (SD), were evaluated by one-way ANOVA. Comparisons between groups were performed using Fisher-test and Student t-test for numerical and categorical data. Multiple correlation analysis were performed using the Pearson's product-moment correlation; Alternative two.sided (r) with appropriate R packages (Biosta TGV) version 3.3 (nlme, multcomp, ggplot2) (R Core Team, 2016). Differences were considered significant when the p value was <0.05.

RESULTS

Physiological and anthropometrical characteristics of the study population

Our study population is divided into 2 groups according to their gestational diabetes status. The first group (G1), considered as control group, includes 25 normoglycemic pregnant subjects without any history of illness or risk factors of gestational diabetes; the second group (G2) includes 35 women with Gestational Diabetes(GD) without any other history of illness except a diabetic pregnancy. To that end, 71% of our GDM mothers have already been background of gestational diabetes in their previous pregnancy.

Furthermore, all pregnant women were between twentieth and thirtieth gestational week. They had no history of smoking and were not taking decoction or medicine which could disturb pregnancy evolution. The anthropometrical and physiological parameters of the study population are shown in Table 1.

Table 1 : Comparison of anthropometrical and physiological data between two groups.

	Age (year)	Weight (kg)	Height (m)	BMI (kg/m²)	HR (BPM)	SBP (mmHg)	DBP (mmHg)	MBP (mmHg)
Controls	28±4	72.3±3.4	1.68±0,03	25.62±1.27	84.36±10.52	120±6	74±6	89±5
GDM	29±3	76.1±5.8	1.7±0.0	26.9±1.3	77.8±4	122±7	72±8	88±7
P value	0.113	0.002	0.488	0.0002	0.0008	0.190	0.154	0.343

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MBP: Mean Blood Pressure, BMI: Body Mass Index, HR: Heart Rate, Control: control group, G1 (n=25), GDM: Gestational Diabetes Mellitus group: G2 (n=35), Data were expressed as mean (M) ± standard deviation (SD), p : P value: significance threshold <0.05

The anthropometric parameters of our study population was matched by age (G1:28±4ans; G2:29±3ans), BMI (G1:25.6±1.27; G2:26.9±1.3) and blood pressure whose values are in normal interval (Systolic BP:[110-132mmHg]; Diastolic BP:[63-87mmHg]; Mean BP:[79-103mmHg]) (Table 1).

Biochemical characteristics of study population

The biochemical profile of the participants is shown in Table 2. Gestational diabetic women exhibited higher fasting glycemia and insulinemia compared with healthy pregnant mothers. With regards to insulinresistance assessment, the HOMA-IR index were significantly higher in GDM women (G1:1.31±1.05; G2:7.4±1.07; p<0.01). Compared to control women, lipid levels were higher in GDM mothers with increase of total cholesterol and triglyceride. Kidney result ((urea: G1:0.12±0.03; G2:0.7±0.03; p=0.20) ; (creatinine:G1:5.97±0.85; G2:6..3±0.8; p=0.05)) had not shown significant difference between groups of mothers (Table 2).
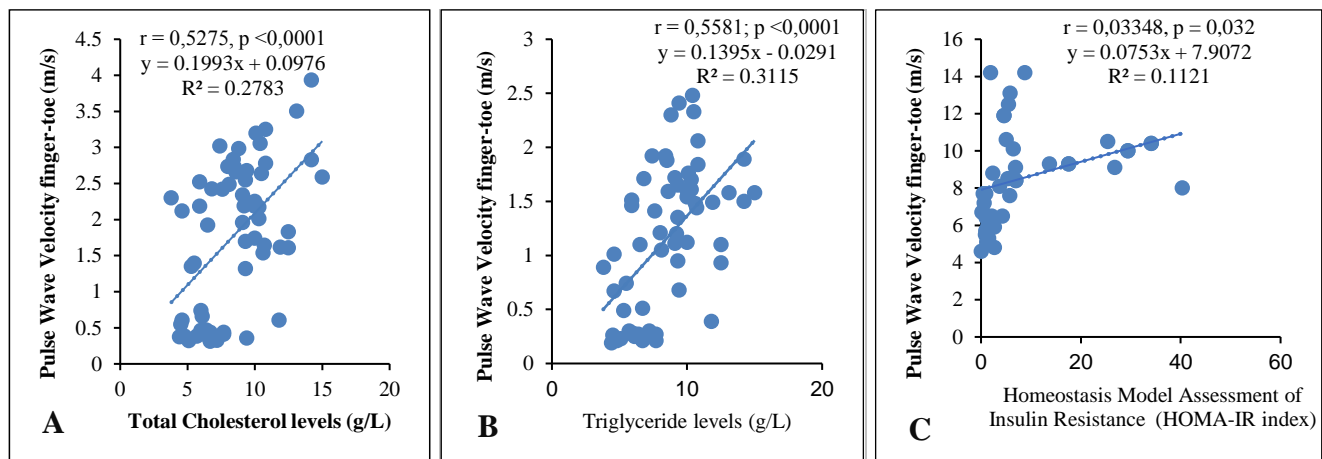
Table 2: Comparison of biochemical and radiological (PWVft) parameters between two groups.

	Control	GDM	P
Glucose (g/l)	0.80 ±0.10	1.5±0.4	<0.0001
Insulin (µUI/ml)	6.35±4.8	31.5±23.3	< 0.0001
HOMA-IR index	1.31±1.05	7.4±1.07	<0.01
Triglycéride (g/l)	0.57±0.04	1.6±0.4	<0.0001
Total cholesterol (g/l)	0.95±0.08	2.4±0.7	<0.0001
HDL cholestérol (g/l)	0.44±0.02	0.76±0.2	<0.0001
LDL cholesterol (g/l)	0.40±0.05	1.3±0.5	<0.0001
Urea (g/l)	0.12±0.03	0.7±0.03	= 0.20
Creatinine (mg/l)	5.97±0.85	6.3±0.8	= 0.05
PWVft (m/s)	5.99±1.23	10.3±1.9	<0.0001

Control: control group : G1 (n=25), GDM: Gestational Diabetes Mellitus group : G2 (n=35), HDL Cholesterol: High Density Lipoprotein cholesterol

HOMA-IR: Homeostasis Model assessment of insulin resistance was quantified following the HOMA-IR index formula: HOMA-IR=Insulin (µUI/mL)×Glucose (mg/dL)/405.[17]

Characteristics of pulse wave velocity in study population

Pulse wave velocity profile of study population

The comparison of pulse wave velocity values between two study groups is materialized in Figure 1. Mean of PWVft was increased in GDM women compared with the control ones (control: 5.99±1.23; GDM:10.3±1.9; p<0.0001).

Relationships between PWVft and metabolic and cardiovascular parameters

Figure 2 shows correlations the between PWVft and other clinical variables. Univariate analyses showed that PWVft was positively correlated with HOMA-IR index (P=0.0323; r=0.3348); Total Cholesterol (P<0.0001; r=0.5275) and Triglyceride (p<0.0001; r=0.5581) (Figure 2).

Figure 1: Comparison of pulse wave velocity finger-toe (PWVft) values between two groups.

The linear regression suggested that HOMA-IR index, Total Cholesterol and Triglyceride were independently associated with PWVft level ((p=.0323; r²=0.1121); (p<0.0001; r²=0.2783) and (p<0.0001 ; r²=0.3115) respectively)) (Figure 2).

r : Correlation coefficient, p : p-value:significant threshold <0.05, R² : Determination coefficient measuring the prediction quality of linear regression
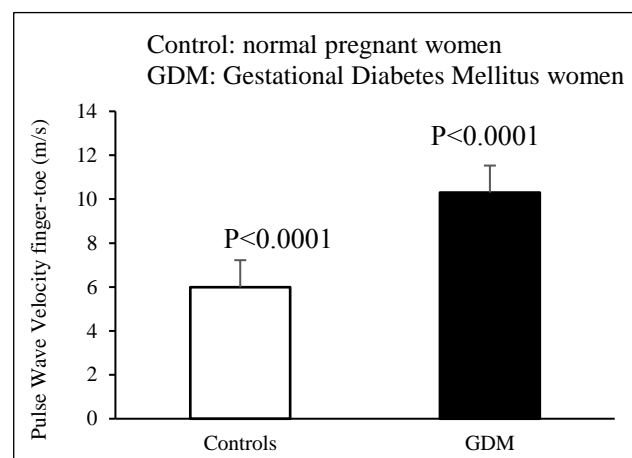
Figure 2 : Relationships between PWVft, cardiovascular risk factors (A, B) and HOMA-IR (C).

DISCUSSION

Our study population involves pregnant women aged from 20 to 35 years old with gestational age, between twentieth four and thirtieth five week of gestational beam without any history of illness or other cardiovascular risk factors. It has been shown that advanced age (>39years), high blood pressure, hypercholesterolemia, tobacco, kidney and cardiovascular diseases affect the vascular function.[18,19] Thus, to make sure that the effect on vessels is due exclusively to GDM, we choosed to exclude pregnant women with other cardiovascular risk which may negatively influence the vascular function.

Concerning the term of pregnancy, studies revealed that circulatory changes occur from third trimester of pregnancy.[20-22,8] So, to have better chance to meet some vasculatory disorder, in our study, we included only pregnant women who exceed 24 gestational weeks.

In an anthropometric view, the two groups of our study population were paired with age and BMI and their blood pressure were in normal reference value. This homogeneity of the study population allowed comparison between groups without influence on the eventual variance of the pulse wave velocity (PWV).

Our results suggest that GDM women were hyperinsulinemic and hyperglycemic reflecting a decrease in insulin sensitivity as evidenced by increase of the HOMA-IR index. Our observations are consistent with outcomes of some authors who found that an HOMA-IR index >2.4 express an underlying insulinresistance.[23,17] About the lipid profile: total cholesterol and triglyceride were increased in diabetic women. This is in accordance with the dyslipidemia and the higher cardiovascular risk usually observed in GDM women.[10,24,25,11]

With regard to the relationship insulin resistance and arterial stiffness occurrence, previous studies have shown that PWV is predictive, beyond the usual risk factors, of cardiovascular mortality in healthy and diseased populations.[26,27] So, it has been found that in patients with impaired glucose tolerance and type 2 diabetes, an increase of 1-m/s in PWV has been shown to be associated with an 8% increase in mortality.[28] This fact prove the interest of assessment of pulse wave velocity in our gestational diabetic population.

The current study exhibits that PWVft is higher in mother with gestational diabetes compared to controls, expressing an increase of arterial stiffness. Our results corroborate previous outcomes finding that pregnant women with GDM and type 2 diabetes exhibit increasing of maternal arterial stiffness.[28-33] Furthermore, several studies have reported that alteration of arterial stiffness occur in subjects with impaired glucose tolerance, polycystic ovaries, and newly diagnosed type 2 diabetes.[34-36]

Moreover, in our study, we found a correlation between PWVft and insulinresistance state of GDM women, as assessed by the level of HOMA-IR index. In other words, pregnancies complicated by insulin resistance are independently associated with enhancement of maternal arterial stiffness. There is also positive correlation between PWVft and the usual risk factors as total cholesterol and triglyceride. Our results could be suggested that maternal arterial stiffness assessed by PWVft can give an index of vascular status and may represent a link among insulinresistance, usual cardiovascular risk, and increased tendency to future cardiovascular disease. The mechanism underlying this association could be the altering of haemodynamic variables in diabetic pregnant women. Our idea can be supported by Rahman et al, who have shown that haemodynamic pathways are altered in diabetes. Among these ones, hyperglycaemia, hyperinsulinemia, chronic low-grade inflammation, lipid modulation, alteration of vascular compliance, contribute to the development of diabetic vasculopathy.[37]

Contrary to this results, Bulzico et al and Salmi et al, investigating arterial stiffness in gestational diabetes, found that their pregnant diabetic women, do not have significant increased arterial stiffness.[38,39] But in their study, patients with any previous glucose impairment were excluded. In other words, their study population was exposed to hyperglycemia only during their present pregnancy contrary to our pregnant diabetic women whose majority of them have history of gestational diabetes in previous pregnancies. Therefore, the paradox between results could be explained by the short time of exposure to hyperglycemia in these pregnant patients with gestational diabetes.

CONCLUSION

In this study, we look for differential in arterial stiffness measurements during normal glucose tolerant pregnancies and gestational diabetes mellitus (GDM). We observed a higher pulse wave velocity (PWVft) and positive correlations of PWVft with insulinresistance index (HOMA-IR) and lipid level in pregnant women with GDM. Therefore, gestational diabetes mellitus (GDM) is associated with a higher PWVft values. Gestational diabetes mellitus (GDM) might induce an increase of pulse wave velocity reflecting the increment of arterial stiffness. This last constitute an underlying cardiovascular risk. The increase in PWVft values may depending on the physiopathological background and the metabolic impairments of patients expressing a greater cardiovascular risk. This is in accordance with the hypothesis that PWV may reflect the early changes of arterial stiffness. These observations may be useful in the early prediction of cardiovascular complications.

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