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Effect of Gestational Insulin Resistance on the Maternal-Fetal Metabolic Homeostasis

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Abstract

Our aim was to determine effects of hyperglycaemia and insulin resistance on proteic, lipidic and hydrocarbon metabolism of gestational diabetic mothers and their newborns.

Results revealed that total cholesterol, LDLcholesterol, triglycerides and Apo B levels, were significantly higher in gestational diabetic mothers group compared to control mothers.

About newborns, cholesterol total and triglycerides were in normal intervals for two groups. Therefore, babies born from diabetic mothers have significant higher levels compared to the control group. Positive correlation has been observed between glucose and other studied parameters (C-peptid, insulin, HOMA-index, total cholesterol, LDL cholesterol, triglycerides, ApoB). Negative correlation has been found between glucose and Apo A1 levels. HDL cholesterol and glucose were also negatively correlated.

Ratio as Apo B/Apo A and Apo A/HDL were similar in the two groups of mothers and their babies. The same LDL/HDL and ApoB/LDL ratio, have been observed between two groups of newborns. In GDM mothers, LDL/HDL ratio was significantly higher and ApoB/LDL ratio was significantly lower.

Our results suggest that, under the impact of gestational hyperglycemia, modulation of biochemical metabolism move in the direction of insulin and C-peptid increasing

and impairment of lipidic metabolism as LDL hypercholesterolemia which express high risk of atherosclerosis. Neonatal hyperinsulinemia arising from maternal hyperglycaemia, tend towards a total hypercholesterolemia and hypertriglyceridemia.

Keywords: gestational insulin resistance - metabolic homeostasis - modulation - diabetic mothers – newborns.

Introduction

Gestational diabetes is a disorder of carbohydrate tolerance leading to hyperglycemia of varying severity, starting or first diagnosed during pregnancy [**1,2].** On the pathophysiological level, it is a complex pathology that combines several components including insulin resistance, inflammation and metabolic disturbances **[3]**.]. As a result, studies have suggested that the association of pregnancy-diabetes, and / or diabetes-hypercholesterolemia would be responsible, among other things, for inflammation and vascular dysfunction **[4,5,6].** This association pregnancy-diabetes seems to increase significantly, the risk of cardiovascular desease occurrence in women with a history of gestational diabetes **[7,8**]. It is characterized by biological modifications such as alterations in the carbohydrate, lipid and sometimes renal profiles. All of these factors contribute to the development of immediate maternal-fetal complications and in the medium and long term **[3].** Thus, gestational hyperglycemia also acts on the metabolic homeostasis of the maternal-fetal unit by modulating it. The objective of our study is to characterize the impact of gestational hyperglycemia on the modulation of the biochemical profile of diabetic mothers and their newborns.

Methods

Type and design of the study

We have processed through a prospective, descriptive and comparative study, carried out in 2 groups, in 2 stages: in antenatal consultation (ANC) and at delivery.

In ANC: The 1st group (G1) or control group, was consisted of normoglycemic pregnancies (n = 28) without any history of pathology or risk factor for gestational diabetes.

The 2nd group (G2) was composed of pregnant diabetic non-obese women (n = 23) free from any other progressive chronic pathology.

At childbirth

. Group 1 (G1) was consisted of normoglycemic mothers and their eutrophic babies.

. Group 2 (G2) have included non-obese diabetic mothers and their babies.

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.

Subjects

The study concerned 51 parturients, including 23 pregnant women (G2) and 28 controls (G1) and their newborns. They were in the 20-36-year-old age group and did not suffer from any progressive chronic pathology other than diabetes discovered during pregnancy.

Were included in this study:

1- Women who have given their informed and written consent

2- Parturients and their newborns, free from all progressive chronic pathologies (hypertension, sickle cell

disease, tuberculosis, HIV, known cardiovascular and systemic diseases) and having presented:

- for group 1 (G1): a normal pregnancy with normal fasting blood sugar levels, without any risk factor for gestational diabetes and regularly monitored in prenatal consultation until delivery.
- for group 2 (G2): pregnancy with gestational diabetes in non-obese women, regularly monitored in prenatal consultation until delivery.

For the two control and diabetic groups, the non-inclusion criteria are as follows:

- Non-consent.
- The existence of a chronic progressive pathology.
- The existence of obesity
- Premature deliveries (before the 37th week of amenorrhea).
- Births by spinal anesthesia or by cesarean section.

For controls: subjects with a risk factor for gestational diabetes are also excluded from the study.

Experimental protocol

Medico-obstetric history and anthropometric variables: During the clinical examination of our pregnant women, we looked for a history of:

- Risk factors linked to gestational diabetes (polycystic ovarian syndrome (SPKO), history of familial diabetes, history of gestational diabetes, advanced age, overweight and obesity….)
- Complications that may result from previous gestational diabetes (arterial hypertension, pre-eclampsia, miscarriages, repeated abortions, stillbirth, macrosomia, cesarean section, etc.)

For the measurement of the anthropometric parameters, we used the following equipment:

- A measuring rod graduated in centimeters, to measure the size of parturients.
- A Terraillon brand bathroom scale to determine the weight of adults in kilograms,
- A centisouple (flexible Bohin centimeter) graduated in centimeter, for the measurements of the newborn.
- A SECA 354 brand electronic baby scale to determine the weight of newborns in grams.
- A data collection sheet where the measured parameters are collected.

The anthropometric and physiological variables studied are: age (in years for mothers and in hours (H1) for babies), weight in kilograms, height in meters, the Body Mass Index (BMI) of the parturients and the cranial perimeter (PC) of newborns. The BMI also called the Quetelet index was calculated from weight (P) and Height (T) using the Quetelet formula: BMI = P (kg) / T^2 (m^2) **[9].**

NB: In mothers, only the weight values taken at the start of pregnancy were taken into account.

Blood samples: Immediately after childbirth, venous samples were taken from the mother and from the umbilical cord blood immediately after delivery and cut of the cord.

Samples were taken from

- gray fluoride tubes (with anti-coagulant sodium fluoride associated with potassium oxalate), the plasma of which collected after centrifugation, will be used for the determination of blood glucose.
- dry tubes (without anti-coagulant) whose serum collected after centrifugation will be used to determine the other biochemical markers targeted in this study.

Biochemical variables

The biochemical parameters were analyzed using the automatic spectrometer: chemistry module LEc4000 of architect system ci4100.

We determined plasma glucose concentrations and serum levels of insulin, C-peptide, Apolipoprotein A1 (ApoA1), Apolipoprotein B (ApoB), triglycerides (TG), total

cholesterol (Tchol), HDL Cholesterol (high density lipoprotein cholesterol (HDLchol)). The concentrations of LDL cholesterol (Low Density Lipoprotein cholesterol (LDLchol)) were calculated using Friedwald's formula: LDLChol = TChol-HDLChol-TG / 5.

The HOMA Insulin Resistance Index (HOMA-IR) was determined using the equation:

HOMA-IR = Insulin (µIU / mL) × Glucose (mg / dL) / 405 **[10].**

Statistics

Statistical analysis was performed using GraphPad Prism version 5.2 software and data expressed as means ± standard deviations (or ± SEM). Fisher's test and Student's t-test were used in comparing the means obtained between the two groups of our study population. Thanks to Biosta TGV version 3.3 software (R Core Team, 2016), we looked for links between quantitative variables by the Pearson correlation (r) associated with the coefficient of determination (R) measuring the quality of the linear regression prediction. The significance level is $p<0.05$.

Results

In order to determine the effects of hyperglycemia and insulin resistance on the protein, lipid and hydrocarbon metabolism of diabetic mothers and their newborns, we carried out biochemical and statistical tests, aimed at determining the modulation the synthesis of peptide-C and insulin as well as the profile of apolipoproteins A1 and B (ApoA1 and ApoB) and lipids (cholesterol (total, HDL, LDL) and triglycerides).

The results obtained are shown in the figures below:

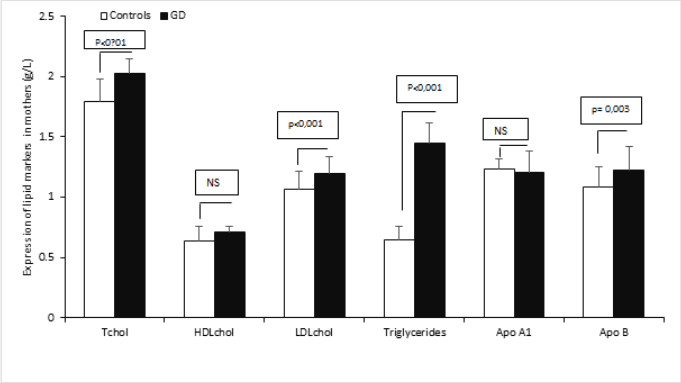


Figure 1: Expression of lipid markers in mothers

DG: group of mothers with Gestational Diabetes

Controls: group of healthy mothers

T Chol: Total Cholesterol

HDLChol: HDL Cholesterol

LDL =Chol: LDL Cholesterol

ApoA1: Apolipoproteins A1

ApoB: Apolipoproteins B

p = significance level

NS = Not Significant

HDL Cholesterol and Apo A1 levels were not different from those in the control group. In contrast, the values of Total Cholesterol, LDL Cholesterol, Triglycerides and ApoB were significantly higher in DG mothers compared to the group of control mothers.

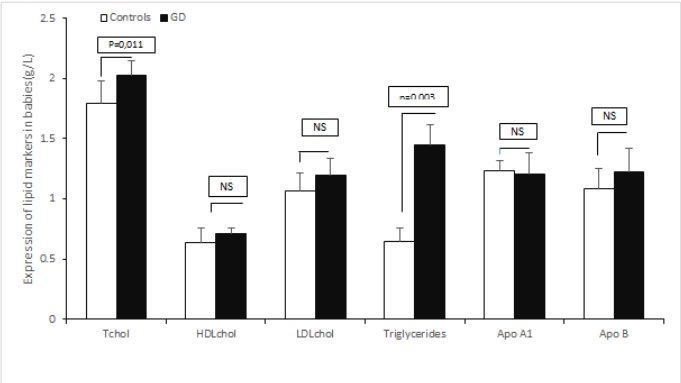


Figure 2: Expression of lipid markers in babies

DG: group of newborns from diabetic mothers

Controls: group of newborns from healthy mothers

TChol: Total Cholesterol

HDLChol: HDL Cholesterol

LDLChol: LDL Cholesterol

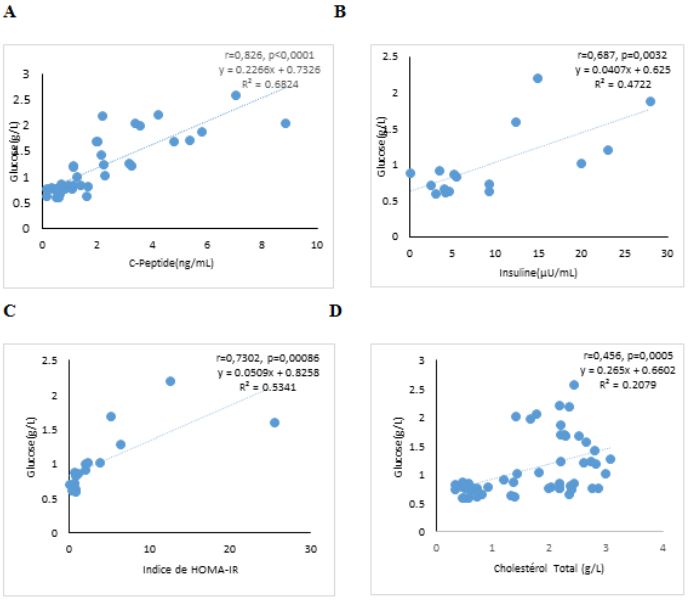
ApoA1: Apolipoproteins A1

ApoB: Apolipoproteins B

p = significance level <0.05

NS = Not Significant

The values of ApoA1, ApoB, HDL Cholesterol and LDL Cholesterol, were not different from those of the control group. However, Total Cholesterol and Triglyceride levels were within normal limits for both groups; but were significantly higher in children of diabetic mothers compared to the control group of children.



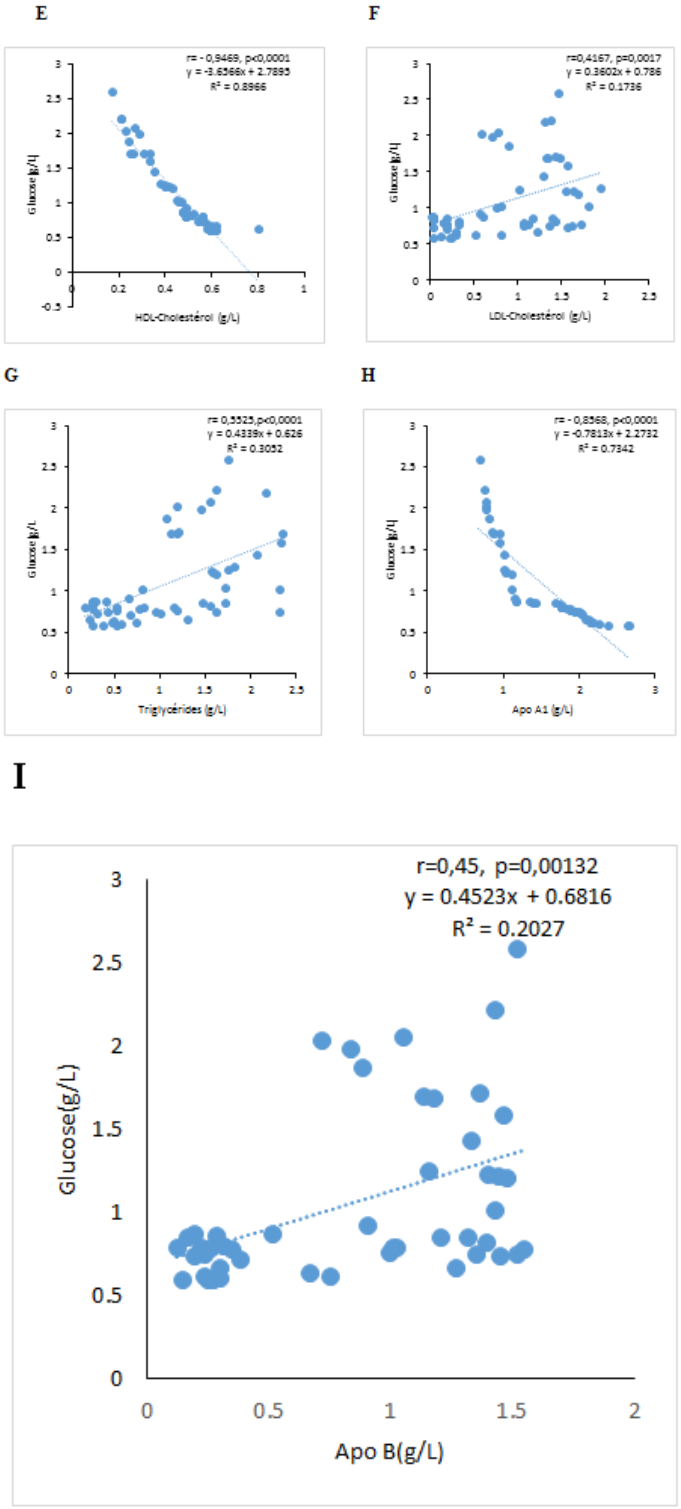


Figure 3: Links between blood glucose and markers of insulin resistance (A, B, C) and lipid metabolism (D, E, F, G, H, I).

r: Correlation coefficient, p: p-value: significance threshold <0.05,

R^2: Coefficient of determination measuring the quality of prediction of linear regression.

ApoA1: Apolipoproteins A1

ApoB: Apolipoproteins B

A significantly positive correlation is observed between the different glucose levels and the parameters studied (C-peptide, insulin, HOMA index, total cholesterol, LDL cholesterol, triglycerides, Apo B).

A negative correlation was observed between glucose levels and Apo A1 and HDL cholesterol.

Table 1: Ratio of lipid markers

	Mothers		Newborns	
	Control	Diabetic	Of control mothers	Of diabetic mothers
ApoB/ApoA1	0.41	0.47	0.42	0.45
LDLChol / HDLChol	1	1.86*	1.06	1.08
ApoA1/HDLChol	2.84	2.76	2.86	2.76
ApoB/LDLChol	1.16	0.97*	1.44	0.94

* : significant difference

HDLChol: HDL Cholesterol

LDLChol: LDL Cholesterol

ApoA1:ApolipoproteinsA1

ApoB: Apolipoproteins B

The ApoB / ApoA, ApoA / HDL ratios were similar in the two groups of mothers as well as in their babies. The LDL / HDL and ApoB / LDL ratios were also identical between the two groups of newborns.

In the group of diabetic mothers, the LDL / HDL ratio was significantly higher and the ApoB / LDL ratio significantly lower.

Discussion

In our study, we have done the relationship between gestational diabetes - insulin resistance - metabolic homeostasis - maternal-fetal biochemical modulation.

Diabetes alters lipid and carbohydrate metabolism over a wide area **[11].** In normal pregnancy, elevation of serum lipids is common in the last trimester of pregnancy **[11].** It has also been shown that the levels of FFA (non esterified Free Fatty Acids), cholesterol and triglycerides increase significantly from the 12th week of gestation **[11].**

In gestational diabetes, many studies have revealed the high cardiovascular risk linked to the occurrence of metabolic disorders including dyslipidemia **[12,7, 13, 14].** Our investigations focused on the search for metabolic changes that could increase or accelerate the risk of cardiovascular abnormalities in diabetic mothers and their offspring.

To this end, we found in our study that the maternal levels of HDL Cholesterol and Apo A1 were not significantly different from those of the control group. On the other hand, the values of Total Cholesterol, LDL Cholesterol, Triglycerides, Apo B were significantly higher in the mothers suffering from gestational diabetes compared to the group of control mothers. The LDL / HDL ratio was significantly higher and the ApoB / LDL ratio significantly lower. This excess of LDL-cholesterol comes from the fact that this molecule comes from the hydrolysis of VLDL-cholesterol under the action of lipoprotein lipase (LPL) **[11].** Insulin, being a major inducer of LPL, will thus promote the production of LDL-cholesterol which has significant atherogenic power **[11].** In addition, numerous studies have shown that the risk of atherosclerosis is linked to an increase in the level of low density lipoproteins (LDL, IDL, VLDL) in plasma **[15].** As a result, a high LDL-C / HDL-C ratio, such as found in our diabetic mothers, is an important predictor of the risk of atherosclerosis.

As for apolipoproteins, they are transporter glucoproteins containing hexosamine, fructose and sialic acid **[11].** ApoB and ApoA1 are structural apolipoproteins. As a result, in their absence, lipoproteins are not synthesized. They reflect the concentrations of particles carrying cholesterol. They thus represent all of the "pro" or "anti" atherogenic cholesterol **[16].**

Apolipoproteins A including apolipoprotein A1 (Apo A1) are present on the surface of neosecreted chylomicrons and HDL-cholesterol, considered to be an anti-atherogenic factor **[17,18].**

As Apo-A is often associated with HDL-cholesterol within anti-atherogenic particles, is therefore considered to be an anti-atherogenic factor **[19].**

Apolipoproteins B (Apo B) are present on the surface of VLDL-cholesterol and LDL-cholesterol, considered to be a pro-atherogenic factor **[17, 18].** Since apo-B is often associated with LDL-cholesterol in atherogenic particles, it is therefore considered to be a pro-atherogenic factor **[19,18].**

In our study, the choice of evaluating (measuring) apolipoproteins A and B and their ratios is justified by the results of some authors. According to them, the degree of coronary artery disease correlates well with the levels of apolipoproteins AI and B **[15].** The measurement of apo B, which better reflects the number of LDL particles, allows a better assessment of cardiovascular risk than that of LDL-cholesterol **[15].** The apoB / AI ratio has been shown to be superior to LDLc as a risk index in several studies **[20,21,22].** Thus, an increase in the Apo B / Apo A ratio is a classic cardiovascular risk factor **[23,24].** This shows the importance of lipoprotein levels and their ratios, such as Apo B / LDL, in assessing the risk of atherosclerosis **[11].** The higher concentrations of Apo B, as found in our diabetic mothers, increase the risk of atherosclerosis **[15]** and thus constitute an index of coronary risk **[16].**

Regarding the newborns of diabetic mothers in our study, the levels of Total Cholesterol and Triglycerides, although within normal limits for both groups, were significantly higher in the children of diabetic mothers compared to the group d. 'control children. These results are in the same direction as those of Pantelakis and Lloyd. According to Pantelakis et al, total lipids, total cholesterol, total phospholipids are all increased for babies whose mothers did not receive insulin **[25].**

According to Lloyd, total cholesterol was significantly higher in the cord venous blood of children of diabetic mothers **[26].**

On the other hand, some authors have found a decrease in HDL cholesterol accompanied by an increase in LDL cholesterol levels and LDL-C / HDL-C and TC / HDL-C ratios **[27].**

In contrast, Pribylova and Fordyce found that Total Cholesterol and triacylglycerol were similar in the two groups of children **[28,29].**

Ultimately, the parameters: triglycerides, total cholesterol and apolipolipoproteins B, although they are high in diabetic mothers, are found at normal levels in newborns with a tendency to total hypercholesterolemia and hypertriglyceridemia compared to to control babies. These observations are consistent with those of Raivio et al **[30].** The latter claims that these molecules cannot cross the foeto-placental barrier due to their large molecular weight. However, maternal, lower molecular weight unesterified FFAs are transmitted to the fetus via the placenta. These FFAs are used in the liver and adipose tissue for the synthesis of triglycerides. In addition, high levels of FFA and insulin increase lipoprotein synthesis at the same time that hyperinsulinemia associated with hypoglycemia inhibits lipolysis **[30].** The excessive production of FFA during pregnancy **[11],** could explain the hypertriglyceridemic tendency observed in newborns. An assay of FFA in these newborns would allow us to better establish this assertion.

The C-peptide produced in an amount equal to that of insulin in the body is the best way to measure endogenous insulin secretion. Thus, the C peptide reflects the potential of the pancreas to secrete insulin during diabetes **[31].**

Furthermore, it has been suggested that fetal hyperinsulinism is assessed by the level of C-peptide in cord blood **[32,33,34].** In our study, a positive correlation between blood glucose levels and those of C-peptide and insulin was observed in both diabetic mothers and their offspring. These results are consistent with data in the literature according to which there is a positive correlation at the 4th quantile between the levels of C-peptide and the level of insulin resistance **[35].** Thus, estimating C-peptide levels, coupled with that of HDL-Cholesterol, constitutes a means of monitoring the insulin resistance.

Conclusion

Our results suggest that, under the effect of gestational hyperglycemia, the modulation of biochemical metabolism is in the direction of dysregulation of the metabolism of carbohydrates in diabetic mothers and their newborns with increased insulin. and its co-factor (C-peptide) and impaired lipid metabolism. The lipid profile of diabetic mothers reveals an alteration of lipid metabolism with predominantly LDL-hypercholesterolemia, predisposing to a high risk of atherosclerosis. Neonatal hyperinsulinemia, consecutive to maternal hyperglycemia, suggests a tendency to total hypercholesterolemia and hypertriglyceridemia.

These newborns should be followed on a longitudinal basis in order to assess the cardiovascular risk in the medium and long term.

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