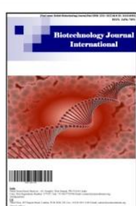

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Effect of Gravidity on Cardiovascular Markers in Normotensive Pregnant Women

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Gravidity, or the number of pregnancies a woman has had, is linked to a number of biochemical alterations, including changes in cardiovascular parameters. These modifications may increase the likelihood of cardiovascular disease in this population. The aim of this research was to evaluate the effect gravidity has on some cardiovascular markers among normotensive pregnant women. A cross-sectional study of 100 women of reproductive age was carried out at Rivers State University and Rivers State University Teaching Hospital, the subjects were chosen at random for the study. Blood samples were taken and tested for total cholesterol, triglycerides, high density lipoprotein, uric acid, and Apolipoprotein A1 and B. Apolipoprotein A1 and B were all measured in blood samples for biochemical analysis. The levels of low density lipoprotein and very low density lipoprotein were determined. Graph Pad Prism Version 8.0.2.263 was used to analyze the data from the study. Result gotten from the study showed that Gravidity had no significant effect on biochemical parameters (TC, TG, UA, LDL, Apo A1, Apo B, CRP, and VLDL) in pregnant women ($P>0.05$), but there was a significant increase ($P<0.05$) in HDL levels among the group; 0.87 ± 0.21 (1-2), 0.93 ± 0.21 (3-4), 0.86 ± 0.12(5-6) and 1.30 ± 0.00 for (7-8). The effect of gravidity (1-2, 3-4, 5-6, 7-8) on HDL was shown to be significant for ANOVA and Turkey post hoc multiple comparison test; (1-2 vs 7-8) ($P= 0.0204$) and (5-6 vs 7-8) ($P= 0.0250$).. This study demonstrated that gravidity had little or no effect on the biochemical parameters but increases the HDL cholesterol level in normotensive pregnant women.

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Keywords: Gravidity; pregnancy; C-reactive protein lipoproteins; apolipoproteins; uric acid.

1. INTRODUCTION

The period when a woman has one or more progenies in her womb is known as human pregnancy, also known as gestation or gravidity. It is usually separated into three trimesters based on gestational age (weeks and months). From conception to 12 weeks is the first trimester (2 months and 3 weeks). The second trimester lasts from 13 to 27 weeks (3 to 6 months and 2 weeks), whereas the third trimester lasts from 28 weeks to birth (7 to 9 months) [1].

According to the Global Burden of Disease (GBD), pregnancy-related mortality decreased from 377,000 in 1990 to 293,000 in 2013, with the most common causes being high blood pressure, maternal hemorrhage, abortion complications, obstructed labor, and maternal sepsis.

Changes in maternal metabolism and body composition occur throughout pregnancy in order to give enough energy and nutrients to the developing child and, later, for nursing. Plasma lipid concentrations rise dramatically as pregnancy progresses, with plasma cholesterol and triglyceride concentrations rising by 25-50 percent and 200-40 percent, respectively [1].

Increased cardiac output and blood volume, widespread vasodilation, lower blood pressure, and resistance to stress hormones such as norepinephrine and angiotensin II are all signs of a healthy pregnancy [2]. According to Neboh and his co-researchers, metabolic changes in normal pregnancy, such as hyperlipidemia, hypercoagulability, and inflammatory states, are exacerbated in preeclampsia and are identical to those linked with an unfavorable risk profile for cardiovascular disease Neboh *et al.,* [3]. In Western countries, cardiovascular disease, such as atherosclerosis, is still the primary cause of death and morbidity. Atherosclerosis is a disease that affects the major arteries [4], and is caused by the interaction of genetic and environmental factors modulating the functions of various different cell types and inflammatory molecules within the wall of the artery [5]. Hyperlipidemia is a primary risk factor for this condition, which can occur as a result of lipoprotein overproduction or decreased clearance from the plasma. Total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG), and very low-density lipoprotein (VLDL) are all lipoproteins that circulate in plasma in complexes that are not attached to albumin [6]. Lipids are transported and delivered throughout the body via plasma lipoproteins.

The acute phase reactant C-reactive protein (CRP) is produced in the liver in response to the cytokine interleukin-6 [7]. It has been hypothesized that C-reactive protein can be produced by smooth muscle cells in human coronary arteries in response to cytokines with inflammatory properties [8] CRP, in addition to being a marker for vascular inflammation, has an active role in atherosclerosis, according to a study by Casas et al., [7]. This is a factor that causes atherosclerotic plaque to progress.

Plasma lipoproteins' main role is to transport hydrophobic lipids like triglycerides and cholesterol to peripheral tissues where they can be stored as energy sources and substrates for steroidal hormone synthesis [9]. Lipoproteins are assembled in two major organs: the liver and the gut. VLDLs (primarily apoB100-containing lipoproteins in humans) are produced by the liver to transport endogenous fat to peripheral organs. In the circulation, these particles are catabolized, resulting in the formation of plasma LDL: Because LDL cholesterol is known to be atherogenic, it is presumed that hepatic lipoproteins are the primary and sole cause of atherosclerosis [4]. In normocholesterolaemic diabetic patients, ApoB100 is related with ischemic heart disease and defines high-risk phenotypes. This could be utilized to determine these patients' lipidaemic profile [10].

Following the fact that metabolic changes occur during pregnancy and possible changes in cardiovascular markers occur, the study focused on evaluating the impact of gravidity on cardiovascular risk markers among normotensive pregnant women in Rivers State.

2. MATERIALS AND METHODS

2.1 Experimental Design

A cross-sectional examination of 100 female respondents was conducted for this study. Subjects were chosen at random from Rivers State University and the Rivers State University Teaching Hospital, and divided into groups based on the number of pregnancies (gravidity) after ensuring that they met the criteria for inclusion.

2.2 Experiment Location

This research was conducted in Rivers State University and the Rivers State University Teaching Hospital, Port Harcourt, Nigeria.

2.3 Eligibility Criteria

2.3.1 Inclusion criteria

This study included healthy pregnant women as ascertained by their healthcare provider and were receiving prenatal care. This study also included pregnant women without a history of surgery or blood transfusions who were not identified as diabetics. After explanation of the research aim and their responsibilities, those who signed their informed consent were chosen.

2.3.2 Exclusion Criteria

Those reported to be ill or had a known history of any infectious infections, underlying chronic illness such as stomach and intestinal illness, those with a history of prenatal hemorrhage, malignancy, tuberculosis, confirmed diabetes, and cardiovascular disease were all excluded from this study. Those who had previously received blood donation, had surgery, or were unable to give informed consent were also excluded from the study.

2.4 Subject Selection

Subjects were chosen at random from Rivers State University using the number selection method outlined by Fyneface *et al*., [11] and Fyneface *et al.,* [12]. The decision was taken at the Rivers State University Teaching Hospital after ensuring that they met the set criteria for inclusion.

2.5 Sample Collection

Venipuncture was used to obtain blood (WHO, 2010). Blood was carefully emptied into plain vacutainer tubes, allowed to clot, then centrifuged for 10 minutes at 1500rpm. The serum was separated and kept at -4°C until it was tested for CRP, apoA1, apoB, uric acid, total cholesterol, triglycerides, and high density lipoprotein cholesterol, as well as the values of LDL and VLDL [13].

2.6 Biochemical Determinations

Biochemical tests for uric acid, Apo A1 and B, CRP, TG, HDL, and total cholesterol were performed on fasting blood samples. All biochemical studies were performed at Rivers State University's Department of Medical Laboratory Science.

Determination of High Sensitive C-reactive Protein Concentration in Human Serum (Nazir & McQueen, [14] method was used).

Procedure

The test tubes were filled with 2µ liters of sample, as well as 5 additional tubes for calibration. To each tube, 250µl of R1 assay buffer was added. It was combined by tilting the bottoms of the tubes, then incubated at 37°C for 5 minutes and the absorbance was measured as OD1. Each tube received 50ul of R2 antibody reagent. It was mixed by tilting the bottoms of the tubes, then incubated at 37°C for 3 minutes and the absorbance was measured as OD2.

Determination of Apo Lipoprotein A1 in Human Serum (The Nazir and McQueen [14] approach was employed).

Procedure

The test tubes were filled with 2µl of serum, and 5 more tubes were used for calibration. 250µl of buffer (R1) was added to each tube, mixed by tilting the bottoms of the tubes, and allowed to sit in a water bath for 5 minutes at 37°C. It was then measured at 340 nm in a spectrophotometer. OD1 was used to represent the absorbance. In a water bath, 50µL of the antibody reagent (R2) was added to the reaction and left to sit for 5 minutes at 37°C. The spectrophotometer was then used to read it at 340nm. OD2 was used to represent the absorbance. The absorbance of the standard and sample was calculated as [OD2– OD1].

Determination of Apolipoprotein B in Human Serum (Nazir and McQueen's [14] approach was employed in this study).

Procedure

The test tubes were filled with 2µ liters of serum, with 5 additional tubes serving as calibration tubes. 250µl of buffer (R1) was added to all of the tubes, mixed by tilting the tubes' ends, and allowed to sit in a water bath for 5 minutes at 37°C. A spectrophotometer with a wavelength of 340nm was used to read it. OD1 was assigned to the absorbance. In a water bath, 50µl of antibody reagent (R2) was added to the reaction and left to sit for 5 minutes at 37°C. The

spectrophotometer was used to read it at 340nm. OD2 was assigned to the absorbance. For samples and standards, absorbance was calculated as (OD2 – OD1). The concentrations of the controls, standard, and sample were determined using a standard curve.

Determination of Total Cholesterol in Serum (Allain *et al.,* [15] technique was used).

Procedure

Conditions for the assay were taken into account. Distilled water was used to zero the instrument. One ml of cholesterol reagent was pipetted into clean dry test tubes labeled blank, standard, and tests, followed by 10 l of distilled water, standard, and sample. It was thoroughly mixed by tilting the bottoms of the tubes, then incubated for 5 minutes in a waterbath at 37°C. In a spectrophotometer set to 540nm wavelength, the absorbance of the standard and test samples was compared to the blank.

Determination of High-Density Lipoprotein (HDL) Cholesterol in Serum (The method of Tietz, [16] was applied).

Procedure

The blood samples were placed in tubes and centrifuged at 12,000rpm for five minutes. The supernatant (sera) was separated and organized into control, standard, and sample tubes according to the labels. 200 liters of precipitating reagent (R) and 20 liters of sample were placed in test tubes, 20 liters of standard in standard tubes, and distilled water in blank tubes. It was properly blended by tilting the bottoms of the tubes and let to stand at room temperature for 10 minutes. The contents of the tubes were centrifuged at 12,000rpm for 2 minutes. After that, the clear supernatant was collected and HDL cholesterol was measured.

Determination of Triglycerides in Serum (The approach of Fraser & Hearne, [17] was employed).

Procedure

Conditions for the assay were taken into account. Distilled water was used to zero the instrument. As a blank, standard, and test, each tube received 1ml of triglyceride reagent. The tubes were filled with 10µl of standard and sample, mixed, and incubated at 37°C for 5 minutes. The absorbance of samples was measured against a blank at 505nm using a 1cm wavelength (cuvette).

Determination of Low-Density Cholesterol ((LDL-C) (The method of Friedwald *et al.* [13] was used)).

Calculation

The difference between the results of total cholesterol, triglycerides, and HDL in the serum sample was used to calculate LDL cholesterol levels.

LDL – Cholesterol = Total Cholesterol – (TG/2.2) – HDL (3.8 - 4.9) mmol/l

Determination of Uric Acid in Serum (The enzymatic technique of Barr [18] was applied).

Procedure

Blank, standard, and test tubes were labeled and were placed accordingly. The blank tube received 20µl of distilled water, the standard tube received 20µl of standard, and the test tubes received 20µl of serum, all of which were correctly mixed by tilting the bottoms of the tubes. At 37°C, it was incubated for 5 minutes. The wavelength was then measured with a spectrophotometer at 520nm.

2.7 Quality Control

For each batch of analysis, two levels of normal and abnormal controls were employed to ensure that the methods worked properly. Checking instrument settings and light source, cleanliness of the equipment used, ensuring the water used was free of pollutants to avoid interferences, confirming reaction temperature, and checking the expiry date of the kit and contents were all other control procedures taken.

2.8 Statistical Analysis

GraphPad Prism Version 8.0.2.263 was used to analyze the data from the study. The data derived from the study were presented as a mean and standard deviation. The one-way analysis of variance was used to compare the means (ANOVA). The Tukey comparison test was also employed. P-values<0.05 were considered statistically significant.

3. RESULTS

Table 1 above shows the effects of gravidity (1-2, 3-4, 5-6, 7-8) on the biochemical parameters (TC, TG, HDL, UA, LDL, Apo A1, Apo B, CRP and VLDL) in normotensive pregnant women.. Gravidity showed a significant effect on HDL with the values 0.87 ± 0.21 (1-2), 0.93 ± 0.21 (3-4), 0.86 ± 0.12(5-6) and 1.30 ± 0.00 for (7-8). There was no significant effect on TC, TG, LDL, UA, CRP, VLDL, Apo A1 and Apo B.

Table 2 represents the ANOVA post hoc using the Turkey multiple comparison test for the influence of gravidity (1-2, 3-4, 5-6, 7-8) on biochemical parameters (TC, TG, HDL, UA, LDL, Apo A1, Apo B, CRP, and VLDL) in normotensives (TC, TG, HDL, UA, LDL, Apo A1, Apo B, CRP, and VLDL). The effects of gravity on HDL (1-2 versus 7-8) (P= 0.0204) and (5-6 vs 7-8) (P= 0.0250) were significant. At P<0.05, there was no significant effect on TC, TG, UA, LDL, Apo A1, Apo B, CRP, and VLDL.

4. DISCUSSION

CRP, TC, TG, LDL, HDL, VLDL, UA, Apo A1, and ApoB biochemical parameters among normotensive pregnant women were evaluated in this study. The subjects that participated in this study were pregnant women that attended the health facility where the research was conducted. Gravidity had no significant influence on biochemical markers in this study, however it did have a significant effect on HDL values of 0.87 0.21mmol/L (1-2), 0.93 0.21mmol/L (3-4), 0.86 0.12mmol/L (5-6) and 1.30 0.00mmol/L (7-8) at p0.05. This could imply that additional pregnancies result in a rise in HDL levels in pregnant women with normal blood pressure.

According to Harvey *et al.*, [19] changes in low and high density lipoprotein cholesterols, as well as triglycerides, which supply energy to the growing fetus, occur during pregnancy. This study, however, did not compare cardiovascular risk indicators between pregnant and non-pregnant women, but rather between the number of pregnancies (gravidity). The average total cholesterol level in the Nigerian population is 3.54±0.14mmol/L, as determined several decades ago. Gravidity resulted in a minor increase in total cholesterol levels above the normal range in the current study: 4.49 ± 0.47 mmol/L (1-2), 4.57 ± 0.56 mmol/L (3-4), 4.54 ± 0.50 mmol/L (5-6), and 5.40 ± 0.00 mmol/L. (7-8). However, at p<0.05, this increase was not statistically significant. This means that in pregnant normotensive women, the number of pregnancies (gravidity) has no effect on total cholesterol levels.

When the body breaks down nucleic acids, which contain organic substances called purines, uric acid is formed. Uric acid is dissolved in the blood, filtered by the kidneys, and excreted in the urine for the most part. The body can manufacture too much uric acid or not filter it out enough at times. High uric acid levels are linked to a number of illnesses, including diabetes, gout, kidney stones, and acute renal failure. The normotensive participants' normal values are within the normal range, and there was no significant difference in uric acid levels across the gravidity groups (p>0.05). As a result, pregnancy has no effect on uric acid levels.

Due to the maternal inflammatory response to the pregnancy, CRP is known to be somewhat higher during pregnancy. Ernest et al. [20], on the other hand, recommended that CRP levels of 2.5 mg/dl and higher should be deemed excessive in pregnant women. CRP levels were also slightly higher above the usual ranges of 4.521.58mg/dl (1-2), 5.392.10mg/dl (3-4), 4.521.45mg/dl (5-6) and 4.800.00mg/dl in this study (7-8). But these values were not statistically significant. CRP levels that are elevated during pregnancy may be a sign of difficulties, but more research is needed to completely understand the role of CRP in pregnancy. Previous research has found that poor lifestyle choices like cigarette smoking are linked to elevated CRP levels, while moderate alcohol consumption and increased physical activity are linked to decreased CRP levels [21, 22]. Ordinary people with CRP levels more than or equal to 2 mg/dl will likely require more intensive heart disease care and treatment. CRP levels that are elevated may play a significant role in identifying people who need more intense therapy or follow-up following heart attacks or operations. CRP levels may also be beneficial in identifying those who are at risk for heart disease when cholesterol levels alone are not sufficient.

ApoA1 was one of the two Apo-lipoproteins studied in this study, with values of 345.90±32.28mg/dl (1-2), 345.40±39.19mg/dl (3-4), 354.90±33.35 mg/dl (5-6), and 385.00±0.00mg/dl (7-8), all of which were higher than the normal level of 225 mg/dl but not statistically significant at p<0.05. This could indicate that the participants are immune to coronary artery disease. According to May et al, [23], Apo A1 is a prominent component of HDL

Table 1. Effect of Gravidity on Biochemical Parameters in Normotensives pregnant women

Parameters	1 – 2	3 – 4	5 – 6	7-8	P Value	F Value
	n = 53	n = 32	n = 13	n = 2		
TC(mmol/l)	4.49 ± 0.47	4.57 ± 0.56	4.54 ± 0.50	5.40 ± 0.00	0.0987	2.152
TG(mmol/l)	1.34 ± 0.29	1.37 ± 0.28	1.42 ± 0.24	1.80 ± 0.00	0.1267	1.950
HDL(mmol/l)	0.87 ± 0.21	0.93 ± 0.21	0.86 ± 0.12	1.30 ± 0.00	0.0215	3.375
LDL(mmol/l)	3.04 ± 0.30	3.05 ± 0.42	3.05 ± 0.44	3.30 ± 0.00	0.7992	0.3362
UA(mg/dl)	4.88 ± 0.70	5.16 ± 0.60	5.00 ± 0.47	4.70 ± 0.00	0.2454	1.407
APoA1(mg/dl)	345.90 ± 32.28	345.40 ± 39.19	354.90± 33.35	385.00 ± 0.00	0.3718	1.055
APoB(mg/dl)	139.70 ± 27.07	141.30 ± 31.35	144.20± 44.52	170.00 ± 0.00	0.5822	0.6543
CRP(mg/dl)	4.52 ± 1.58	5.39 ± 2.10	4.52 ± 1.45	4.80 ± 0.00	0.1586	1.767
VLDL(mmol/l)	0.61 ± 0.13	0.62 ± 0.13	0.64 ± 0.11	0.81 ± 0.00	0.1267	1.950

Table 2. Gravidity on Biochemical Parameters in Normotensive Pregnant Women: ANOVA Post-Hoc Findings Using Turkey Multiple Comparison Test

Parameters	1-2 vs 3-4	1- 2 vs 5-6	1-2 vs 7-8	3-4 vs 5-6	3-4 vs 7-8	5-6 vs 7-8
TC(mmol/l)	0.9002	0.9919	0.0648	0.9970	0.1130	0.1139
TG(mmol/l)	0.9642	0.7943	0.1036	0.9486	0.1500	0.2737
HDL(mmol/l)	0.5752	0.9974	0.0204	0.7165	0.0628	0.0250
LDL(mmol/l)	0.9983	0.9993	0.7483	>0.9999	0.7837	0.8054
UA(mg/dl)	0.2124	0.9288	0.9799	0.8734	0.7585	0.9264
APoA1(mg/dl)	0.9999	0.8363	0.4030	0.8361	0.4006	0.6637
APoB(mg/dl)	0.9955	0.9667	0.5297	0.9924	0.5848	0.6921
CRP(mg/dl)	0.1261	>0.9999	0.9961	0.4387	0.9672	0.9968
VLDL(mmol/l)	0.9642	0.7943	0.1036	0.9486	0.15	0.2737

and has been found to predict short- and long-term risk in patients with normal HDL. The HDL levels in this study were lower than normal, which might be due to a change in HDL composition, but Apo A1, which is the primary protein component of HDL and is mostly responsible for reverse cholesterol transport, was found to be lower than normal. Apo A1 essentially reflects the functional status of the HDL molecule. Apo A1 has a consistent inverse connection with CAD occurrences, according to May *et al*, [23], which means that an increase in Apo A1 will always result in a decrease in CAD events.

The Apo B readings in this study were 139.70±27.07mg/dl (1-2), 141.30±31.35mg/dl (3-4), 144.20±44.52mg/dl (5-6), and 170.00±0.00mg/dl (7-8), all of which were somewhat higher above the normal range but not statistically significant at $p<0.05$. According to the American Diabetes Association, [10], the Apo B concentration represents the quantity of atherogenic particles (VLDL, IDL, and LDL). According to Harvey *et al*. [19] this reflection is closely associated with atherosclerosis. Because VLDL-C particles are removed considerably faster than LDL-C particles, Apo B levels in essence reflect LDL-C levels, while high Apo B levels represent a relative fall in cholesterol levels, resulting in small dense LDL-C particles formed from VLDL-C over synthesis.

5. CONCLUSION

Findings from this study have shown that gravidity has little or no effect on the biochemical parameters of normotensive pregnant women but induces higher levels of HDL in these women. Therefore, increase in the number of pregnancies increases HDL levels in normotensive pregnant women.

6. LIMITATION

There were dearth studies in this area.

DISCLAIMER

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

The protocol for this study was approved by the Rivers State Ministry of Health's Ethics Committee in Port Harcourt, Nigeria. Written informed permission for this trial was obtained from participating subjects. Throughout the study, relevant confidentiality was maintained. All of the ladies in this study provided all relevant demographic information.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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