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LIPID PROFILE OF HEALTH WOMEN DURING NORMAL PREGNANCY

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Summery

The four basic lipid indexes (Chol, Trig, HDL-C and LDL-C) are increasing during pregnancy, following different rates of increase. Among the four analytes Triglycerides have the large increase and HDL-C the smaller one. All analytes' values are increasing during the 40 weeks of pregnancy except HDL-C which during the second trimester is stabilized. After delivery, the values are falling except LDL-C which remains steady (for some weeks) before starting to fall following the others. In this study the relations between the four lipid indexes and some predisposing factors (age, gestational age, nationality, Body Mass Index, profession, smoking and diabetes of pregnancy) were investigated. The sample consisted of 413 pregnant women, mainly Greeks and Albanians. After regression analysis it was proved that the only common predisposing factor was the gestational age. Triglycerides and total Cholesterol are influenced also by the women's age. The lipid indexes had no important difference between the pregnant women of the first trimester and the non pregnant women. On the contrary, there was statistical difference between pregnant woman of the second and the third trimester and between them and the first trimester. The percentages of increase between first and second trimester were: Chol: 38%, Trig: 115%, HDL-C: 30%, LDL-C: 33%. The percentages of increase between first and third trimester were: Chol: 65%, Trig: 208%, HDL-C: 26%, LDL-C: 64%.

Key words

Pregnancy, Dyslipidemia, Cholesterol, Triglycerides, High Density Lipoprotein, Low Density Lipoprotein.

Introduction

More than 200 millions women become pregnant every year and in most cases the outcome of labour is successful. Because of the hormonal status changes during pregnancy, various adaptive mechanisms initiate due to sex hormones. Among them, it is observed the alteration of the energetic metabolism to lipid metabolism. That is, pregnant women undergo a physiological dyslipidemia (1) that can be measured in the laboratory by the lipid indexes: total Cholesterol (Chol), Triglycerides (Trig), high density lipoprotein (HDL-C) and low density lipoprotein (LDL-C). The alterations of serum lipid indexes are associated with the gestational age.

The increase of the lipid and lipoprotein metabolism came to the level of cardiovascular risk (2, 3, 4, 5) during the second trimester. Especially, the second and third trimester of human pregnancy is characterized by 2 - 3 fold increases in plasma Triglycerides and lesser increases in total Cholesterol, HDL-C and LDL-C.

Analytically, the average serum LDL-C concentration increases at about 0,80 mmol/L in the second trimester compared with the first trimester and 0,69 mmol/L in the third trimester compared with the second trimester (6). The major increase of the serum Cholesterol concentration is occurring in the second trimester (25 – 50%). The serum Triglycerides concentration is increasing more intensively than all the others and its major increase is occurring during the third trimester (about 200 - 300%) (7, 8). Serum HDL-C concentration is increasing during the second trimester but is decreasing during the third trimester (3). Just after delivery the values of all lipid indexes are decreasing (still remaining above the non-pregnant values) except LDL-C values which remain constant (3).

Women with increase in low-density lipoprotein during the second and third trimester show a more marked increase in serum Triglycerides. That effect is slightly more evident in the multiparous subjects. The observed changes in low-density lipoprotein patterns during pregnancy may be used to identify those women who later in life will have pathologically high low-density lipoproteins. The pregnant women are affected by a type VI hypertriglyceridemia, according to the Fredrickson/WHO classification of hyperlipoproteinemias, with an increase in chylomicrons and VLDL-lipoproteins. This subtype is characterized by the presence of hypertriglyceridemia associated with hypercholesterolemia.

During early pregnancy there is an increase in body fat accumulation, associated with both hyperphagia and increased lipogenesis. The increased lipid production during pregnancy is necessary as energy stores to fulfill maternal and fetal metabolic needs while maternal hypertriglyceridaemia, especially towards late gestation, has an important role as a source of triglycerides for milk formation just before parturition (2). During late pregnancy there is an accelerated breakdown of fat deports, that plays a key role in fetal development. Moreover, using placental transferred fatty acids the fetus benefits from

two other products: glycerol and ketone bodies. Although maternal glucose is quantitatively the main substrate crossing the placenta, glycerol is the preferential substrate for maternal gluconeogenesis. Additionally, enhanced ketogenesis under fasting conditions and the easy transfer of ketones to the fetus allow maternal ketone bodies to reach the fetus, where they can be used as fuels for oxidative metabolism as well as lipogenic substrates.

Although maternal cholesterol is an important source of cholesterol for the fetus during early gestation, its importance becomes minimal during late pregnancy, due to the high capacity of fetal tissues to synthesize cholesterol. Maternal hypertriglyceridemia is a characteristic feature during pregnancy and corresponds to an accumulation of triglycerides not only in very low-density lipoprotein (VLDL-C) but also in low (LDL-C) and high-density lipoprotein (HDL-C). Although Triglycerides do not cross the placental barrier, the presence of lipoprotein receptors in the placenta, together with lipoprotein lipase, prospholipoproteins A2 and intracellular lipase activities, allows the release to the fetus of polyunsaturated fatty acids transported as triglycerides in maternal plasma lipoproteins (9).

The hyperlipideamia of the second half of pregnancy may be a purely physiological response to pregnancy or may be indicative of pathology in some women. It must be investigated whether the hyperlipidaemic response to pregnancy is variable or no and if so, whether it can predict future hyperlipidaemia in a manner analogous to that of impaired glucose tolerance during pregnancy, predicting non-insulin dependent diabetes in later life. There is evidence that triglycerides' concentration, if measured between 9 and 12 weeks of gestation, has moderate predictive value for subsequent glucose tolerance in pregnancy. For that reason further studies are need to investigate the role of early measurement in the screening and management of cardiovascular damage (8, 12).

Late pregnancy is associated with the formation of susceptible, oxidisable particles and an increase in oxidative damage. These biochemical changes may be relevant for the long-term cardiovascular health of women, especially those of high parity who are at high risk for cardiovascular disease (e.g. women with diabetes) (6, 11).

The atherogenic lipid profile of human gestation is further enhanced in preeclampsia. This may be a potential contributor to endothelial cell dysfunction. Studies have shown (12, 13, 14) that in preeclampsia, plasma lipids climb substantially above levels seen in normal pregnancies. Such lipids changes may play a role in the endothelial damage characteristic of preeclampsia.

The high levels of lipid indexes raise two questions: whether hypercholesterolemia and hypertriglyceridemia of pregnancy must be cured or not and whether the pregnancy is atherogenic or not. In pregnancy the elevated levels of Cholesterol are partially a result of high levels of HDL-C, which theoretically are not associated with increase risk of coronary heart disease. Furthermore, hypertriglyceridemia is a controversial risk factor for coronary heart disease. In case those drugs are

necessary, then the statins will be the drugs of choice in hypercholesterolemia along with fibrates for combined hypercholesterolemia and hypertriglyceridemia. There are limited data to suggest that these drugs are not major human teratogens, however it is not recommended to use them during pregnancy (10).

Both Cholesterol and Triglycerides concentration decrease significantly within 24 hours of delivery and this is reflected in all lipoproteins. However, while triglycerides levels continue to decrease rapidly returning to non-pregnant levels during the puerperium, LDL-C remain elevated for at least six to seven weeks postpartum (9, 15, 16). Hyperlipideamia during pregnancy is not related to the nationality (16, 17).

Our study accomplished three different purposes, which were:

Firstly, the study of the alterations of Chol, Trig, LDL-C and HDL-C during the three trimesters of pregnancy. The values of each trimester were compared to the non pregnant women and to the other two trimesters.

Secondly, the estimation of any statistical models which correlate the values of Chol, Trig, LDL-C and HDL-C with a number of predisposing factors such as age, gestational age, nationality, profession, diabetes, smoking and BMI.

Finally, the estimation of reference values for Chol, Trig, LDL-C and HDL-C for each trimester of pregnancy separately.

Material – methods

The samples of pregnant and non pregnant women

Our study is based on women who came for prenatal tests in the gynecological offices and laboratories of the local medical centre of the Social Security Institute of Greece[1]. We used two samples, one of 413 pregnant women (Table I) and another of 102 non pregnant women (Table II). The women of the second sample were the control group of our study. All women were living in the island of Zakynthos. In both samples we got information about Chol, Trig, HDL-C and LDL-C values, age, gestational age, nationality, Body Mass Index (BMI), profession, smoking and diabetes of pregnancy.

According to the nationality the sample of pregnant women consisted of 386 Greeks, 301 Albanians and other ten nationalities (Table III). They were all living in Greece many years.

[1] The Social Security Institute is the largest public insurance organization in Greece. More than a half of Greek population is insured in it (about six million people) and the majority of foreign immigrants.

According to the profession our sample consisted of 219 contemporary clerks (tourist and agricultural jobs), 109 employees, 71 housekeepers, 8 teachers, 2 businesswomen (trade), 2 doctors, 1 gymnast and 2 students. As far as smoking is concerned 348 women never had smoked, 30 had quitted after pregnancy, 27 continued with less smoking and 8 continued to smoke regularly. From the 413 pregnant women only 5 had diabetes of pregnancy.

On the other hand the sample of the 102 non pregnant women (controls) consisted of 62 Greeks, 35 Albanians and other 5 women of three other nationalities. The majority was working as contemporary clerks (51), employees (23), students (2) and businesswomen (1). The majority was non smokers and their Body Mass Index varied from 19 to 24.

	Population (N)	Mean age (years)	Range of age (years)	Mean week of pregnancy
Controls (no pregnant)	102	28,8 ± 6,2	18 – 45	-
Pregnant 1st trimester	355	28,3 ± 5,4	18 – 43	8
Pregnant 2nd trimester	189	29,5 ± 5,9	19 – 45	22
Pregnant 3rd trimester	223	28,8 ± 5,6	18 – 46	32

Table I
Demographics of pregnant and no pregnant women.
The majority of pregnant women are in the first trimester.

	Population	Average & standard deviation (mmol/L)	Range of Values (mmol/L)	Median (mmol/L)
Chol	102	4,66 ± 0,54	3,46 - 5,72	4,63
Trig	102	1,01 ± 0,35	0,41 – 1,79	0,97
HDL-C	101	1,42 ± 0,30	0,83 – 2,24	1,37
LDL-C	101	2,75 ± 0,57	0,30 – 3,95	2,81

Table II
Descriptive statistics of Chol, Trig, HDL-C, LDL-C of no pregnant women (controls).

Greeks	386
Albanians	301
Britains	27
Bulgarians	13
Rumanians	10
Serbians	8
Italians	8
Germans	4
Poles	4
Turks	3
Indians	2
Russians	2

Table III
The nationalities of pregnant women.

Chemical analysis

For each woman whose we determined the values of Cholesterol, Triglycerides, HDL-C and LDL-C. Sampling was done in the morning after twelve hours' fast. Cholesterol was measured by the enzymatic end point method CHOD-POD, triglycerides were measured by the enzymatic glycerol Phosphate oxidase / peroxidase method, HDL-C by an homogenous enzymatic direct assay and LDL-C by Friedewald calculation: LDL-C = Chol – [HDL-C- Chol] – Trig / 5 (18, 19).

Statistical analysis

Data were gathered in Rxcel sheets and analyzed in the Minitab statistical software package. The statistic analysis included descriptive statistics (e.g. medians, ranges, percentiles), non-parametric statistics (Mann-Whitney and Kruskal-Wallis test), normality test (Kolmogorov-Smirnov) and regression methods (stepwise method, backward elimination method and forward elimination method) (20).

Results and Discussion

The comparison of Chol/Trig/HDL-C/LDL-C between the three trimesters of pregnancy

We studied statistically the differences of Chol/Trig/HDL-C/LDL-C between pregnant and non pregnant women for each trimester separately. We also compared the lipid values between the three trimesters. According to the Tables IV – VII the values of the four analytes were increasing during pregnancy very intensely. The percentages of increase between first and second trimester were: Chol: 38%, Trig: 115%, HDL-C: 30%, LDL-C: 33%. The increase between second and third trimester was even higher: Chol: 65%, Trig: 208%, HDL-C: 26%, LDL-C: 64%. Triglycerides were proved to show the largest increase during pregnancy.

The medians of Chol/Trig/HDL-C/LDL-C of pregnant (separately in three trimesters) and the non pregnant women were compared with the non parametric test statistics “Mann Whitney” and “Kruskal-Wallis”. Both tests compare the medians of the two or more groups of values.

Chol	Population	Mean (mmol/L)	Median (mmol/L)	Range (mmol/L)	Percentage of increase
1st Trimester	158	4,55 ± 0,78	4,45	3,22 – 7,02	-
2nd Trimester	111	6,19 ± 1,35	6,14	3,17 – 10,22	38%
3rd Trimester	144	7,25 ± 1,27	7,33	4,08 – 10,92	65%

Table IV

Descriptive statistics of Cholesterol versus the trimester of pregnancy. The percentage of increase has been calculated against the first trimester.

Trig	Population	Mean (mmol/L)	Median (mmol/L)	Range (mmol/L)	Percentage of increase
1st Trimester	150	0,88 ± 0,36	0,75	0,41 – 2,18	-
2nd Trimester	100	1,67 ± 0,59	1,62	0,46 – 3,71	115%
3rd Trimester	82	2,40 ± 0,84	2,31	0,5 – 5,48	208%

Table V

Descriptive statistics of Triglycerides versus the trimester of pregnancy. The percentage of increase has been calculated against the first trimester.

HDL-C	Population	Mean (mmol/L)	Median (mmol/L)	Range (mmol/L)	Percentage of increase
1st Trimester	157	1,50 ± 0,34	1,45	0,94 – 2,49	-
2nd Trimester	111	1,87 ± 0,39	1,90	0,83 – 3,07	30%
3rd Trimester	144	1,87 ± 0,39	1,84	1,04 – 2,94	26%

Table VI

Descriptive statistics of HDL-C versus the trimester of pregnancy. The percentage of increase has been calculated against the first trimester.

LDL-C	Population	Mean (mmol/L)	Median (mmol/L)	Range (mmol/L)	Percentage of increase
1st Trimester	158	2,65 ± 0,68	2,6	0,83 – 4,94	-
2nd Trimester	111	3,53 ± 1,01	3,48	1,48 – 3,48	33%
3rd Trimester	144	4,26 ± 1,09	4,26	2,03 – 7,51	64%

Table VII

Descriptive statistics of LDL-C versus the trimester of pregnancy. The percentage of increase has been calculated against the first trimester.

Analytically:

a. The mean value of **total cholesterol** increased in each trimester (Table IV, Figure 1). In the first trimester there was no statistical difference between the values of pregnant and non pregnant women (P = 0,31). On the contrary, between non pregnant and pregnant of second and third trimester there was large statistical difference (P < 0,0001). There was also statistical difference between pregnant of second and third trimester (P < 0,0001). Cholesterol values climbed over the upper reference value (5,69 mmol/L) in 15th week of pregnancy (Figure 1).

b. The mean value of **triglycerides** was also increasing in each trimester (Table V, Figure 2). The medians of the each trimester's values differed (statistically importance difference) from the median of the non pregnant women. There was also statistically important difference between the three trimesters. Triglyceride values were going over the upper reference value (2,28 mmol/L) in 27th week of pregnancy (Figure 2).

c. **High density lipoprotein** had similar attitude with cholesterol (Table VI, Figure 3). The trimester's medians were increasing gradually. There was no statistical difference between the median of the first trimester and the median of the non pregnant women (P = 0,084). On the contrary, the second and third trimester were statistical different from the non pregnant women (P < 0,0001). Between third and second trimester there was no statistical difference (P = 0,7140) but there was a statistical difference between them and the first trimester. According to Figure 3, all HDL-C values were over the upper reference value (0,90 mmol/L).

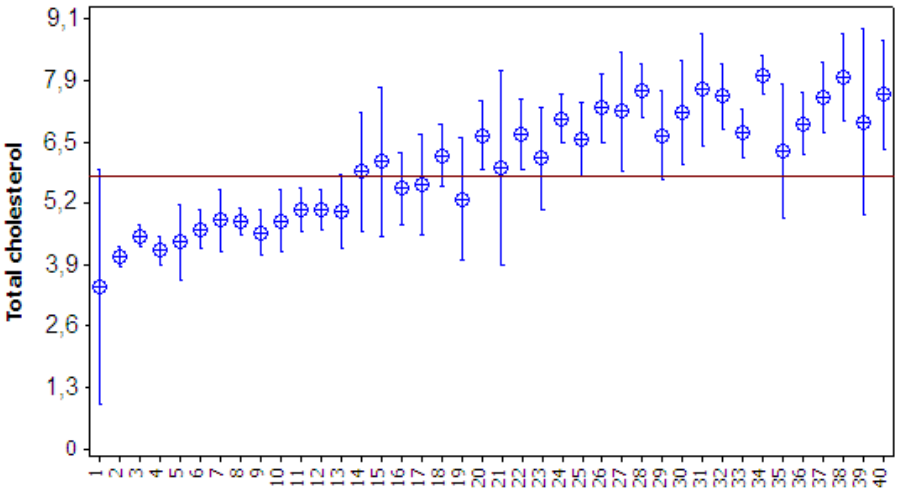

Figure 1
Interval plots of total Cholesterol versus the week of pregnancy. The upper reference value of total cholesterol has also been plotted (5,69 mmol/L). Total cholesterol is going over the upper reference value after the 13th week.

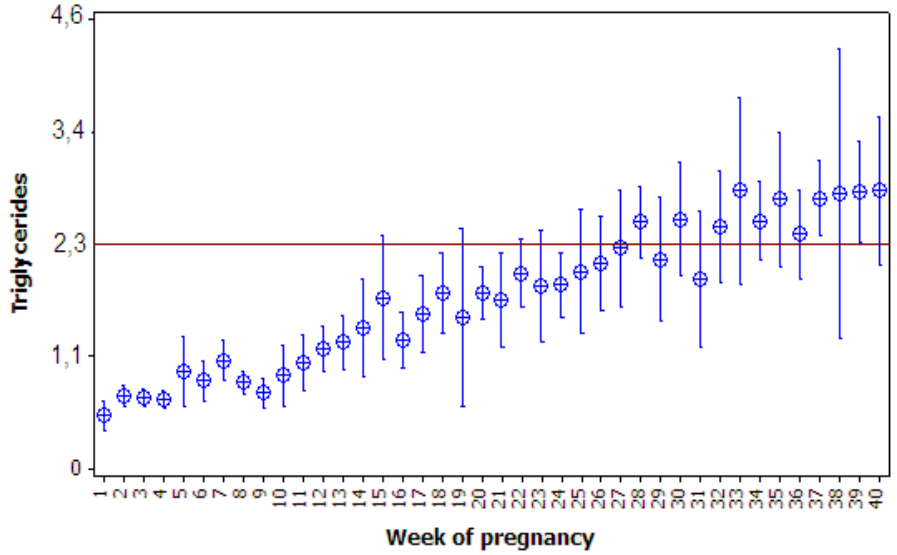

Figure 2

Interval plots of Triglycerides versus the week of pregnancy. The upper reference value of Triglycerides has also been plotted (2,28 mmol/L). Triglycerides are going over the upper reference value after the 27th week.

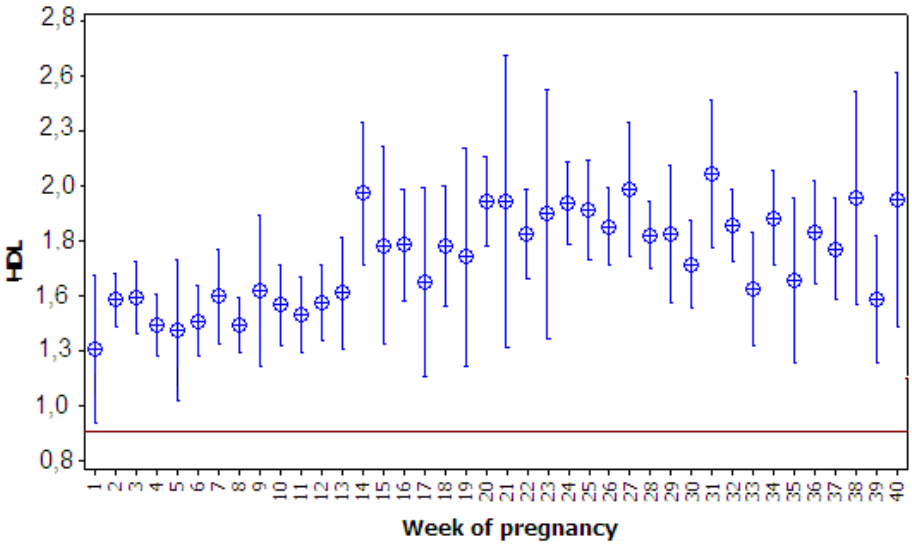

Figure 3

Interval plots of high density lipoprotein (HDL-C) versus the week of pregnancy. The lower reference value of HDL-C has also been plotted (0,90 mmol/L). HDL-C values are always over the lower reference value.

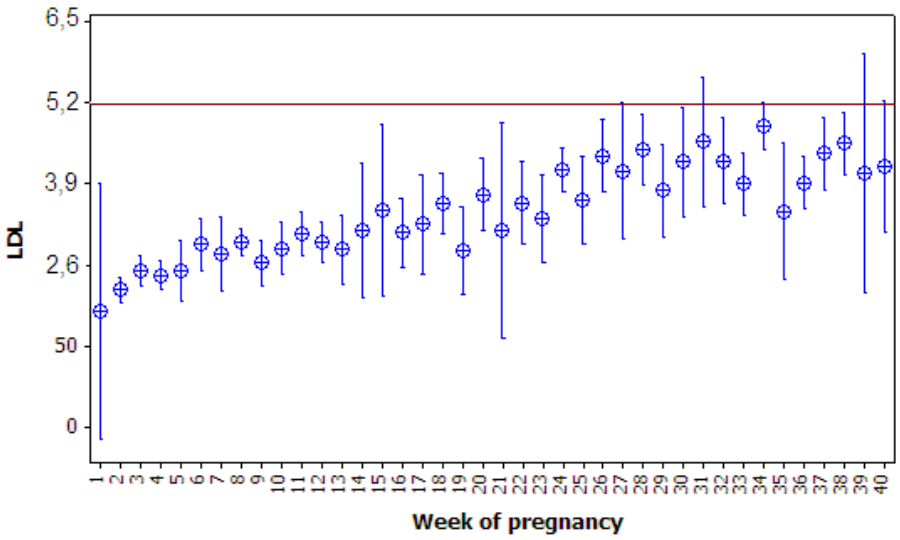

Figure 4

Interval plots of low density lipoprotein (LDL-C) versus the week of pregnancy. The upper reference value of LDL-C has also been plotted (5,18 mmol/L). LDL-C values are always under the upper reference value.

d. **Low density lipoprotein** had similar attitude with Cholesterol (Table VII, Figure 4). Its values were increased in reletion to the week of pregnancy but they remained within the reference values (< 5,18 mmol/L). The median of the first trimester had no statistical difference with the median of the non pregnant women (P = 0,07). The values in the other two trimesters were statistically different from no pregnant women (P < 0,0001). There was also large statistical difference between the three trimesters (P < 0,0001). All LDL-C' values were below the upper reference value (5,2 mmol/L).

e. We also studied separately the atheromatic indexes Chol/HDL-C (Figure 5) and LDL-C/HDL-C (Figure 6). Both were increasing during pregnancy but their values remain below the upper limit of their reference values (5 for Chol/HDL-C and 4 for LDL-C/HDL-C).

In Figure 7, there are the scatter plots of all lipid indexes versus the week of pregnancy. All lipid indexes have positive correlation, although it is very week. The statistic r^2 (coefficient of determination) is always under 50% except from Triglycerides which have coefficient of determination r^2 equal to 59%.

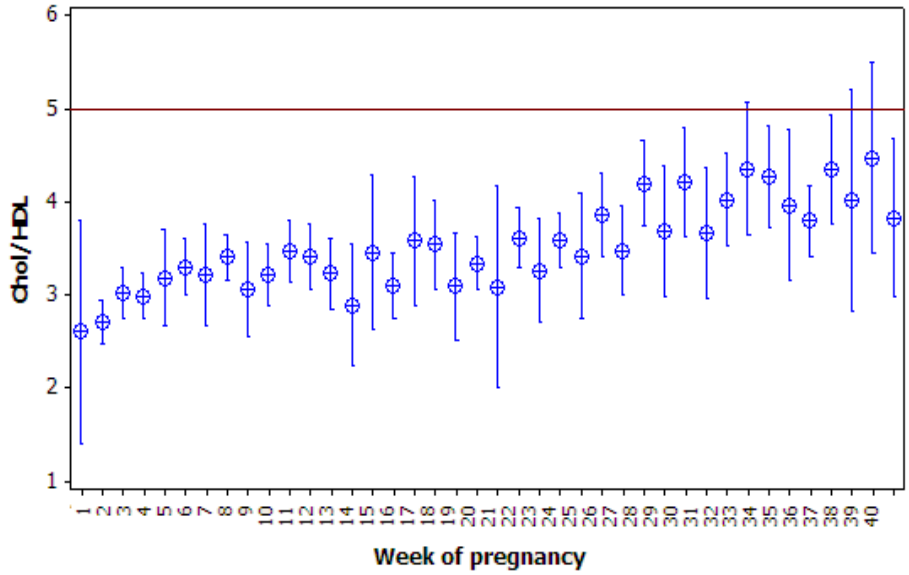

Figure 5
Interval plots of the atheromatic index Chol/HDL-C versus the week of pregnancy. All values are under the upper value which is equal to 5.

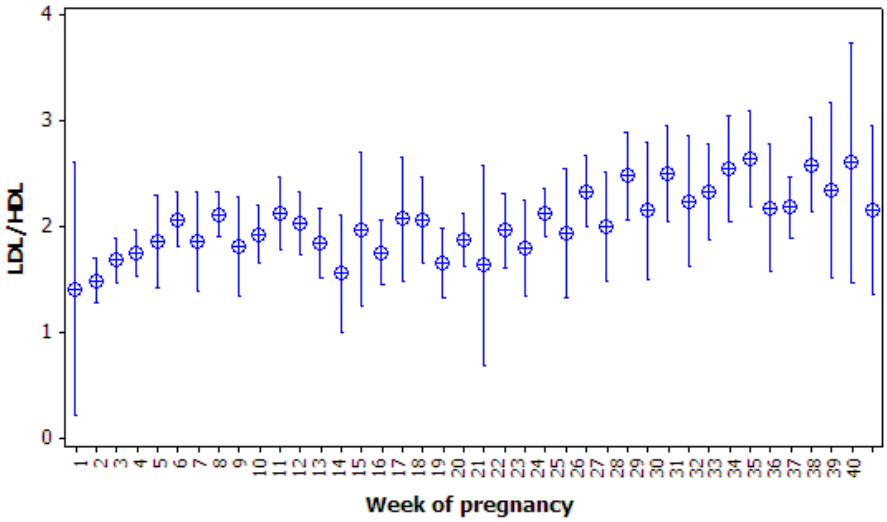

Figure 6
Interval plots of the atheromatic index LDL-C/HDL-C versus the week of pregnancy. All values are under the upper value which is equal to 4.

Parameters and models that explain the values of Chol/Tri/HDL-C/LDL-C during pregnancy

The second purpose of our study was to find out which of the predisposing factors influence the values of Chol, Trig, HDL-C και LDL-C (except, of course, the gestational age). The predisposing factors considered were: age, gestational age, nationality, Body Mass Index (BMI), profession, smoking and diabetes of pregnancy.

The first approach of this study was the estimation of the descriptive statistics of the lipid indexes. Their descriptive statistics, especially box-plot graphs, gave an idea about any relations between large groups of pregnant women.

For instance, the influence of the nationality to the lipid indexes is displayed on Figure 8. As shown there was no important difference between the larger national groups of our sample (Greek, Albanian, Bulgarian, Rumanian, British). Because of the graphs in Figure 8 that include all the pregnancy trimesters, we analyzed our data further with another block of box plot graphs (Figure 9). In these three box-plots, the total Cholesterol's values of the three trimesters have been pictured. As shown there was no important difference between the three professions. However, the median value of the employees was larger from the median of the contemporary clerks.

To find out exactly the parameters which influence the values of Chol, Trig, HDL-C and LDL-C we tried to estimate statistical models which involve them with some predisponsing factors. The following statistical models were investigated by three different regression methods (stepwise method, backward elimination, forward elimination method). The final model includes the most common predisposing factors of the three.

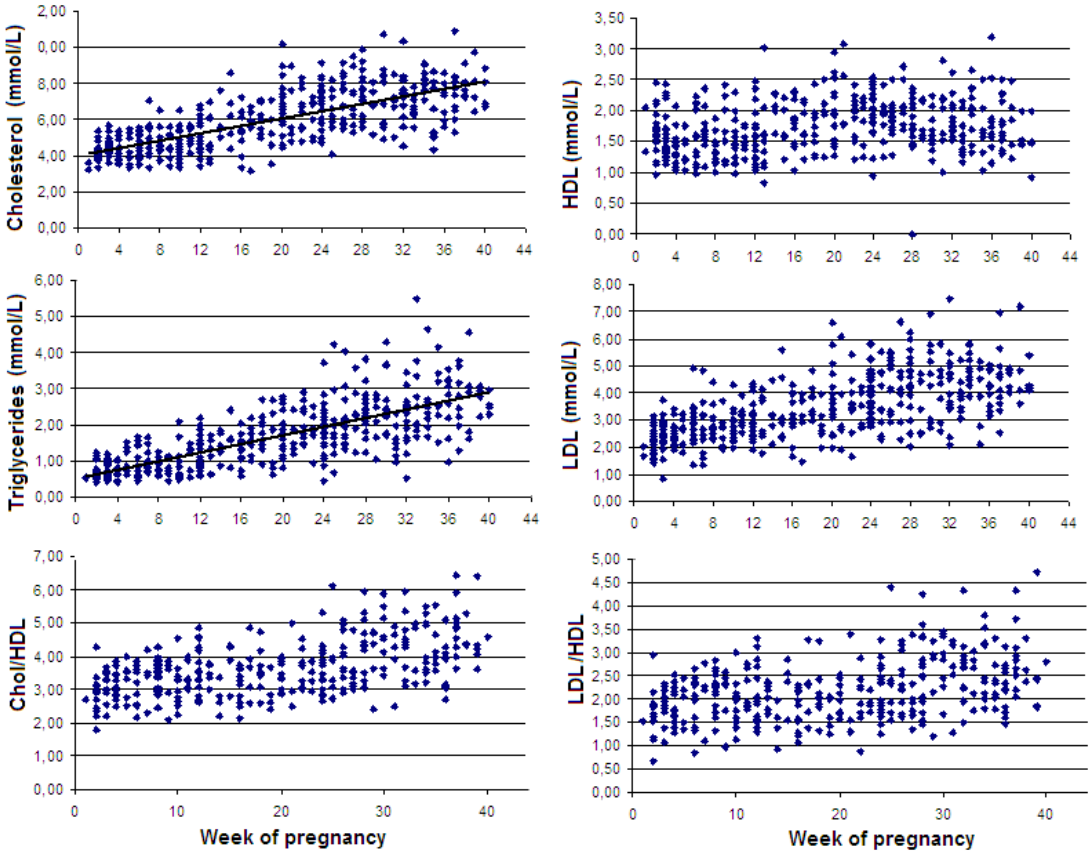

Figure 8

Scatter plots of all the lipid indexes versus the week of pregnancy. Although, all lipid indexes have positive correlation, only Triglycerides have r^2 more than 50% (59%).

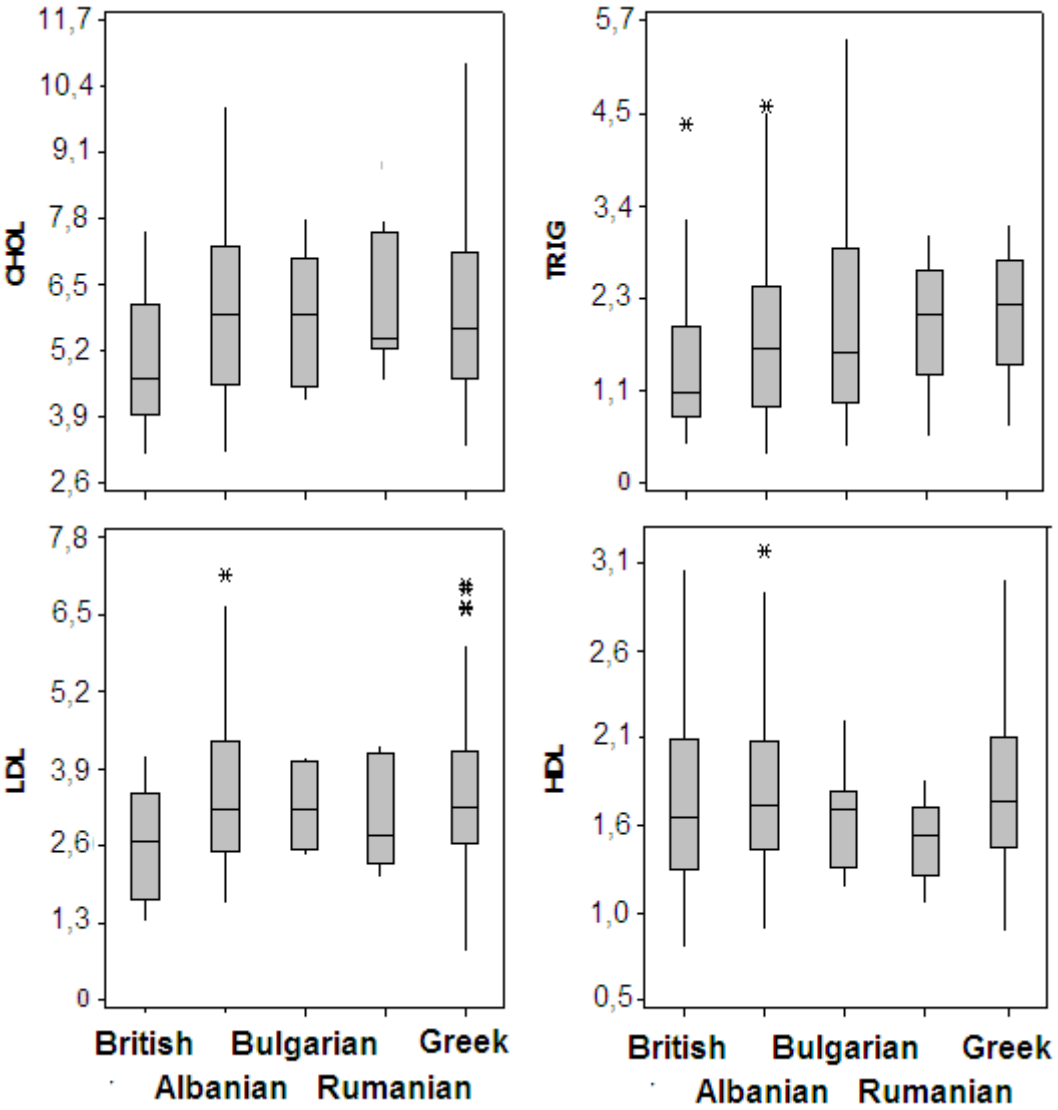

Figure 8
Box-plots of Chol/Trig/HDL-C/LDL-C versus the nationality of the pregnant women

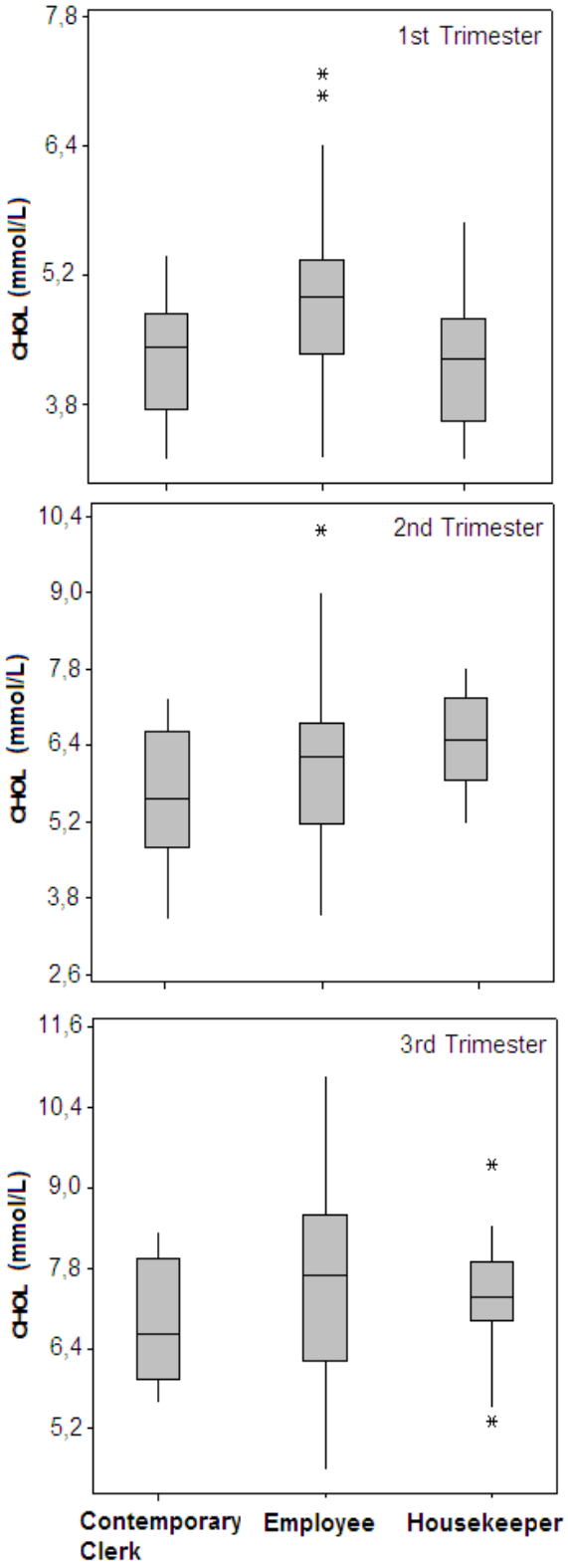

Figure 9
Box-plots of total Cholesterol versus the three professions with the larger frequency. All subjects were Greeks.

Analytically:

Total Cholesterol. The common predisposing factors in the three regression methods were chronic age and gestational age. So they must be considered as the most reliable predisposing factors for the explanation of Cholesterol's values. The regression model between Cholesterol and age/gestational age was: Cholesterol = 5 age + 4,4 gestational age. This model shows that cholesterol values are influenced by age and gestational age with the same percentage. However, the coefficient of determination (r^2) of the model was too low (only 13,7%). As a result the model was not considered reliable.

Triglycerides. The three regression models we used, proved that only two predisposing factors were common to the all of them, chronic age and gestational age. The best model which explained triglyceride values was: Trig = 1,59 age + 5,9 gestational age. The coefficients of this model (1,59 and 5,9) showed that Triglycerides are more influenced from the gestational age. The r^2 of the model was only 55,6%, which means that only the 55% of Triglyceride values can be explained from chronic age and age of pregnancy.

High Density Lipoprotein. From the three regression methods we used, only one predisposing factor appeared in all three models, the gestational age. The most suitable statistical model was: HDL-C = 56,9 + 0,53 gestational age. The r^2 was too low (only 13,7%). As a result the model was not considered reliable.

Low Density Lipoprotein. Regression analysis showed that LDL-C like HDL-C depended only in one of the studied predisposing factors, the gestational age. The most suitable statistical model was: LDL-C = 87,9 + 2,40 gestational age. The model is not reliable since the r^2 was just 38,1%.

Reference values per trimester

We tried to find out reference values for Chol, Trig, HDL-C and LDL-C separately for each trimester. Firstly, the distribution of values was checked by using the statistical test Kolmogorov-Smirnov. It proved that all lipid index' values differed a lot from the normal distribution. For that reason the calculation of reference values was based on non parametric methods (percentiles 2,5 and 97,5). The results are synopsized in the Table VIII. In order to calculate them all subjects that had a pathological predisposing factor were excluded.

	Chol (mmol/L)	Trig (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
1st Trimester	3,98 – 6,52	0,62 – 1,78	1,25 – 2,34	2,23 – 4,29
2nd Trimester	5,22 – 8,97	1,33 – 2,77	1,58 – 2,65	2,78 – 5,80
3rd Trimester	6,37 – 9,83	1,89 – 4,38	1,58 – 2,60	3,43 – 6,68

Table VIII
Reference values of Chol, Trig, HDL-C and LDL-C separately for the three trimesters of pregnancy.

Generally, our results confirmed previous references. Lipid indexes were increasing during pregnancy, although in the first trimester there was no important difference between pregnant and non-pregnant women for the majority of indexes. Triglycerides proved to have the largest increase. Triglycerides were the only lipid index that had statistical important difference between the pregnant of first trimester and the non pregnant women. On the other hand, HDL-C had different profile from the others. It increased during first and second trimester but remained steady during the third trimester. It must be underlined that the relation between the lipid index' values and the week of pregnancy was too weak, although they had an apparently positive correlation. The positive correlations had very small coefficient determinations (under 50%).

Regression analysis showed that the predisposing factors studied (age, gestational age, nationality, Body Mass Index, profession, smoking and diabetes of pregnancy) had no important influence on the lipid index values. Except gestational age, only total Cholesterol and Triglycerides were influenced also by the chronic age. However, all these relations were not strong (under 50% except Triglycerides). As a result all the models we manufactured were not reliable. Additionally, nationality and profession had no important influence on the lipid index values. Considering the foreign nationalities of the sample, it may be assumed that their long stay in Greece (for many years) conducted them to adapt the way of life of the locals.

The last scope of our study was to calculate reference values for each trimester separately. Although all subjects with pathological predisposing factors were excluded from the calculations, the results must be considered absolutely reliable only after prior execution of further studies with larger samples from different populations of women.

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