



THE LONG TERM EFFECT OF MATERNAL OLIVE OIL SUPPLEMENTATION ON METABOLIC AND REDOX STATUS IN OFFSPRING OF OBESE RATS

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The aim of this study was designed to determine whether maternal supplementation with olive oil influence plasma lipid profile and oxidant/antioxidant status later in life of rats with cafeteria- diet-fed during gestation and in their offspring throughout adulthood. Altering the fatty acid profile of rat diets during the gestation has long-term consequences for the growth and development of their offspring. Our results clearly demonstrate that maternal intake of olive oil before gestation, during gestation and during lactation display remarkable health benefits for the prevention of obesity and associated metabolic disorders by decreasing the lipoprotein metabolism and oxidant/antioxidant status alterations brought about by obesity in offspring at birth until adulthood.

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adverse effects of maternal obesity on offspring metabolism have been demonstrated, including increased adult body weight and fat mass, reduced insulin sensitivity, increased blood glucose and triglycerides levels, increased lipid deposition and defects in fatty acids metabolism in adult liver, as well as increased leptin levels.^{8,9} Intrauterine oxidative stress can be generated by maternal over nutrition, which increases risk of adult disease.¹⁰

More recently, attention has shifted towards the role of individual components of the maternal diet in affecting fetal and neonatal development. Polyunsaturated fatty acids (PUFA), in particular the ω -3 PUFA alpha-linoleic acid (ALA) and ω -3 long-chain PUFA (LC-PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), play an important role in fetal development.

It has been reported that a diet enriched in omega-3 long chain polyunsaturated fatty acids (ω -3 LC-PUFA) administered to gestating rats protected against metabolic syndrome which reduced cardiovascular risk.^{11, 12}

Olive oil, the main source of fat in the Mediterranean diet, is rich in unsaturated fatty acids, mainly oleic acid, and phenolic compounds, which contribute to its cardioprotective effects, and has several health benefits prior and during pregnancy on obesity development in offspring.^{13,14,15}

Here, we aimed to assess whether supplementation of maternal cafeteria diet with olive oil before and during gestation has any effect on plasma glucose, lipid profile, and oxidant-antioxidant status of offspring.

Experimental

Animals and Experimental Protocol

Female Wistar rats (aged 1 months, n = 40), weighing 90 to 100 g each, were obtained from Animal Resource Centre (Algeria).

Introduction

Obesity is a major public health issue in both industrialized and semi-industrialized nations across the world, in part because of increasing adoption of a Western diet, high in saturated fat.^{1,2} The development of obesity often results in the onset of further metabolic complications, including insulin resistance and cardiovascular diseases, together termed as metabolic syndrome. Several abnormalities in lipid metabolism have been observed including elevated low-density lipoprotein (LDL) cholesterol, triacylglycerols and apolipoprotein B, and lower high density lipoprotein (HDL) cholesterol concentrations.

Additionally, many studies have shown that obesity is coupled with altered redox state and increased metabolic risk.^{3,4} Oxidative stress can be a consequence but also a trigger of obesity.

Whilst many factors contribute to the development of obesity, there is now an increasing amount of evidence that maternal nutrition during pregnancy and/or lactation is directly related to the adequate development of the fetus, newborn and future adult, likely by modifications in fetal programming and epigenetic regulation, which induce phenotypic changes.⁵

In humans, offspring of obese mothers seem to have increased insulin resistance already at birth, indicating very early life effects on offspring metabolic profile and oxidative stress status.^{6,7} In experimental animals, several

Animals were housed at 20 ± 2 °C with 2-3 in each cage, and maintained on a 12:12 h light/dark cycle. Rats were assigned to each diet group during 8 weeks of experimental period. The control group (control, C, $n=10$) was fed standard laboratory chow (ONAB, Algeria) before and during pregnancy. The second group (cafeteria group, CAF, $n=10$) was fed a fat-rich hypercaloric diet before and during pregnancy. In group three (control olive, CO, $n=10$) rats were on standard chow supplemented with olive oil (5 %) before and during pregnancy. In group four (cafeteria olive oil 5 % (CAFO, $n=10$), rats were on cafeteria diet supplemented with olive oil (5 %) before and during gestation.

The control diet (386 kcal 100 g⁻¹) was composed of 20 % of energy as protein, 20 % of energy as lipids and 60 % of energy as carbohydrates. The components of the cafeteria diet were grinded pâté, cheese, bacon, chips, cookies and chocolate (in a proportion of 2:2:2:1:1:1, by weight) and control diet (mix/control diet) as published previously.¹⁶ The composition of the cafeteria diet (523 kcal 100 g⁻¹) was 16 % of energy as protein, 24 % of energy as carbohydrates and 60 % of energy as lipids. The composition of the four diets is listed in (Table 1). Pure olive oil was obtained from INRA (INRA, Algeria). Fresh food was given daily and body weights were recorded.

After mating, the first day of gestation was estimated by presence of spermatozooids in vaginal smears. Pregnant dams of each group were maintained on their respective diets throughout pregnancy and lactation. After delivery, the newborn rats were continued to feed similar diet of their mothers.

The study was conducted in accordance with the national guidelines for the care and use of laboratory animals. All the experimental protocols were approved by the Regional Ethical Committee.

Blood samples

At birth (day 0), 20 newborn rats in each group (control and experimental) were killed by decapitation, and blood was collected by pooled from four animals as per the protocol of Garcia-Molina et al to obtain sufficient serum samples for chemical determinations.¹⁷

On days 30 and 90 for pups, eight rats from each group were anesthetized with intraperitoneal injection of sodium pentobarbital (60 mg kg⁻¹ of body weight). The abdominal cavity was opened and blood was drawn from the abdominal aorta into EDTA tubes. Blood samples were centrifuged to obtain plasma for glucose, lipids, and oxidant/antioxidant status parameters determinations. After removal of plasma, erythrocytes were washed three times with two volumes of isotonic saline solution. Erythrocytes were lysed with ice-cold distilled water (1/4), stored in the refrigerator at -4 °C for 15 min and the cell debris were removed by centrifugation (2000 g for 15 min). Erythrocyte lysates were assayed for antioxidant enzyme activities.

Chemical analysis

Plasma glucose, total cholesterol (TC), and triacylglycerols (TG) were measured using enzymatic assays kit (Sigma). Plasma creatinine, uric acid and urea were measured using enzymatic colorimetric methods (Kits from BioAssay Systems, CA). Plasma aspartate aminotransferase (AST) (EC 2.6.1.1) and alanine aminotransferase (ALT) (EC 2.6.1.2) activities were determined by the colorimetric method using Randox Diagnostic kits (Randox Laboratories Ltd, Co Antrim, UK), with an interassay CV of 2.8 %.

Table 1. Composition of experimental diets.

Component	Energy sources (% energy)			
	C	CO	CAF	CAFO
Protein	19	18.5	20	20
Carbohydrate	60	60	24	24
Fat	10	10	50	50
Olive oil	/	05	/	5
Vitamin (mg 100 g ⁻¹)	1	1	1	1
Energy values (kcal 100 g ⁻¹)	386	386	523	523
% Fatty acids				
SFA ^α	27	22	42	39.5
C _{18:1} n-9 ^β	24	30	30	33
C _{18:2} n-6	45	44	27	26.5
C _{18:3} n-3	3	3	1	1
C _{20:4} n-6	1	1	0	0

Note: The control and cafeteria diets, in powder form, were supplemented with the purified oils as indicated. α : saturated fatty acids. β : monounsaturated fatty acid Fatty acid composition was analyzed by gas liquid chromatography, INSERM UMR 866, "Lipids Nutrition Cancer", University of Burgundy, France.

Plasma lipoprotein (LDL $d = 1.063$, HDL $d = 1.21$ g mL⁻¹) were separated by sequential ultracentrifugation in a Beckman ultracentrifuge (Model L5-65, 65 Titorot), using sodium bromide for density adjustment. HDL cholesterol and LDL cholesterol concentrations were also measured by enzymatic kits (Sigma).

Erythrocyte reduced glutathione (GSH) was determined using 5, 5-dithiobis-2-nitrobenzoic acid (DTNB or Ellman reagent).¹⁸ Superoxide dismutase (SOD) (EC 1.15.1.1) activity was measured by the NADPH oxidation procedure.¹⁹

The radical nature of NOS and its short half-life make the measure of its production so difficult. Thus the determination of stable products of NOS, nitrite and nitrate, is used to determine NOS concentration. The procedure comprises two steps; the first step consists in chemical reduction of nitrate to nitrite by cadmium, followed by the spectrophotometric detection of nitrite at 540 nm.²⁰

Superoxide level determination in plasma was based on the superoxide anion mediated nitro blue tetrazolium (NBT) reduction to monofarmazan, a chromophor that absorbs at 550 nm.²¹

Table 2. Body weight of the studied rats.

Sample	Control rats		Cafeteria obese rats		p (ANOVA)
	C	CO	CAF	CAFC	
Mothers					
BW before pregnancy	164.70±3.08 ^c	161.14±1.25 ^c	244.38±2.91 ^a	186.39±1.78 ^b	0.0001
BW at the end of pregnancy	219.39±10.09 ^b	216.47±4.12 ^b	331.33±2.80 ^a	210.26±5.36 ^b	0.0001
Offspring					
BW at birth	4.90±0.35 ^c	5.42±0.64 ^b	7.97±0.28 ^a	5.93±0.54 ^b	0.0001
BW on 30th day	57.04±4.00 ^b	68.16±4.62 ^b	78.5±1.87 ^a	70.83±3.60 ^b	0.0001
BW on 90th day	190.48±2.36 ^b	196.5±13.08 ^b	266.83±6.49 ^a	261±3.34 ^a	0.0001

Note: BW = body weight in g. Values are presented as means ± standard deviations (SD). C: rats fed control diet, CAF: obese rats fed cafeteria diet, CO 5 %: rats fed control diet enriched with olive oil at 5 %, CAFO 5 %: obese rats fed cafeteria diet enriched with olive oil at 5 %. Values with different superscript letters (a, b, c, d) are significantly different ($P < 0.05$).

Statistical analysis

Results are expressed as means ± standard deviation (SD). The results were tested for normal distribution using the Shapiro-Wilk test. Data not normally distributed were logarithmically transformed. Significant differences among the groups were analyzed statistically by a one-way analysis of variance (ANOVA). When significant changes were observed in ANOVA tests, Fisher least significant difference tests were applied to locate the source of significant difference. The individual effects of the diets and the oil supplementations were distinguished by two-way ANOVA. The significance level was set at $P < 0.05$. These calculations were performed using STATISTICA version 4.1 (STATSOFT, Tulsa, OK).

Results

Body weight

The cafeteria diet consumption led to significantly higher body weight as compared with standard chow in both mothers and their offspring. However, supplementation with olive oil at 5 % induced a significant reduction in body weight in both control and obese rats of mothers and their offspring ($p = 0.0001$) but had no effects on the offspring of CAFO group at the ages of 1 and 3 months (Table 2).

Plasma biochemical parameters

Plasma glucose, urea, creatinine, uric acid, AST and ALT activities were significantly higher in diet induced obese rats fed on basal cafeteria diet (CAF). Oil supplementation induced a significant reduction in CAF group but had no effects on the CO group. Neither the cafeteria diet nor oil supplementation affected APL activities in the offspring, as revealed by 2-way ANOVA (Table 3).

Lipid and lipoproteins concentrations

Blood levels of triglycerides and cholesterol decreased in the group fed with olive oil compared with the other samples (Table 4). We also note a decrease in LDL-C in the offspring of control rats and rats treated with olive oil compared with obese rats. However, the plasma levels of

HDL-C are increased in control rats and rats treated with olive oil compared to obese rats in offspring at birth (Table 4).

Oxidative stress biomarkers

Erythrocyte antioxidant enzyme activities were markedly different among the four groups studied. The SOD and GSH activities were significantly higher ($p < 0.05$) in rat adult offspring feeding with cafeteria. The administration of olive oil at 5 % to obese rats leads to an increase in GSH and SOD activities in both control (CO) and obese treated rats (CAFO). There is no significant difference of oxidants and antioxidants results in offspring at birth and at weaning (Figure 1). A significant increase was observed in the levels of plasma NO, O₂ in cafeteria group compared to control group and supplemented groups with olive oil (CO, CAFO) (Figure 2).

Discussion

The intake of an excess of fat during pregnancy and lactation may have negative consequences on the metabolic health of offspring in the long term. In the present study, a palatable cafeteria diet was given to dams 8 weeks before mating to induce long-term dietary obesity in breeders. Maternal cafeteria diet feeding induced a marked reduction in body weight, an increase in serum glucose, cholesterol, triglyceride, urea acid, urea, creatinine, aminotransferases and lipid concentrations in offspring at birth and they remained obese throughout adulthood, in agreement with previous studies.^{8,9}

A higher foetal weight of high fat fed dams may be caused by changes in nutritional transport through placenta, either up-regulation of specific nutrition's like glucose and amino acids indicating from higher protein gene expression of glucose transport Glut 4 and sodium coupled neutral amino acid transport SANAT 2 or either to the ability of placenta to take up chylomicron remnants core lipids by increasing mRNA expression of fatty acid oxidation protein PPAR rather than fatty acid transport.^{22,23} Currently, we know that a diet rich in saturated fatty acids might lead to changes in the action of insulin, with hyperglycemia, increased body mass, and a systemic pro inflammatory state, which can be transmitted to other generations.²⁴

Table 3. Effect of the different diets on the biochemical parameters of the offsprings.

Parameter	Control rats		Cafeteria obese rats		P (ANOVA)
	C	CO	CAF	CAFO	
At birth					
Glucose (mg dL ⁻¹)	64.02±1.21 ^d	89.62±1.02 ^b	92±1.16 ^a	85.07±0.72 ^c	0.0001
Creatinine (mg dL ⁻¹)	4.08±0.31 ^c	4.00±0.24 ^c	6.46±0.35 ^a	5.17±0.33 ^b	0.0001
Uric acid (mg dL ⁻¹)	22.80±0.91 ^b	23.07±2.04 ^b	56.34±2.84 ^a	26.57±3.25 ^b	0.01
Urea (mg dL ⁻¹)	17.10±0.01 ^b	17.71±0.91 ^b	36.19±0.92 ^a	19.02±0.99 ^b	0.0001
GTO (UI L ⁻¹)	31.99±0.71 ^c	31.98±0.71 ^c	51.51±0.67 ^a	41.02±0.74 ^b	0.0001
GTP (UI L ⁻¹)	28.04±2.68 ^c	26.99±1.01 ^c	42.79±0.76 ^a	32.65±0.91 ^b	0.0001
ALP (UI L ⁻¹)	86.17±4.47 ^a	88.29±3.48 ^a	84.83±5.20 ^a	86.92±4.18 ^a	0.2438
Day 30					
Glucose (mg dL ⁻¹)	79.83±7.13 ^c	90.45±13.98 ^b	100.29±4.61 ^a	81.36±4.47 ^c	0.0001
Creatinine (mg dL ⁻¹)	5.33±0.33 ^b	5.07±0.13 ^b	7.98±0.10 ^a	5.65±0.45 ^b	0.01
Uric acid (mg dL ⁻¹)	35.38±0.93 ^b	39.19±1.64 ^b	72.77±1.82 ^a	39.44±2.73 ^b	0.0001
Urea (mg dL ⁻¹)	22.34±6.20 ^c	23.97±1.72 ^c	58.66±2.44 ^a	29.73±0.96 ^b	0.0001
GTO (UI L ⁻¹)	36.86±4.00 ^b	34.11±3.18 ^b	50.51±0.71 ^a	40.03±3.04 ^b	0.0001
GTP (UI L ⁻¹)	26.99±1.02 ^d	32.65±0.91 ^c	49.15±0.83 ^a	41.51±0.99 ^b	0.0001
ALP (UI L ⁻¹)	100.77±3.87 ^a	103±5.44 ^a	99.76±1.53 ^a	101.10±4.11 ^a	0.4152
Day 90					
Glucose (mg dL ⁻¹)	87.2±8.53 ^b	86.33±8.18 ^b	140±11.33 ^a	121±17.43 ^a	0.0001
Creatinine (mg dL ⁻¹)	9.3±0.42 ^b	9.63±0.47 ^b	12.16±0.87 ^a	9.95±0.95 ^b	0.0001
Uric acid (mg dL ⁻¹)	47.66±1.82 ^b	44.48±1.43 ^c	57.74±4.35 ^a	40.70±1.89 ^c	0.0001
Urea (mg dL ⁻¹)	25.38±1.00 ^b	26.52±1.11 ^b	54.12±0.72 ^a	26.74±0.83 ^b	0.0001
GTO (UI L ⁻¹)	46.85±0.58 ^c	44.05±0.68 ^c	56.40±0.70 ^a	51.14±0.81 ^b	0.0001
GTP (UI L ⁻¹)	42.45±1.47 ^b	42.06±1.34 ^b	52.94±0.88 ^a	41.54±5.29 ^b	0.0001
ALP (UI L ⁻¹)	83.35±4.15 ^b	87.66±2.80 ^a	84.34±4.62 ^b	88.33±3.83 ^a	0.0341

Note: Values with different superscript letters (a, b, c, d) are significantly different ($p < 0.05$).

Table 4. Lipid and lipoprotein concentrations in the offsprings.

Parameter	Control rats		Cafeteria obese rats		P (ANOVA)
	C	CO	CAF	CAFO	
At birth					
TG (mg dL ⁻¹)	30.10±2.16 ^b	23.46±3.03 ^c	56.28±1.78 ^a	33.45±2.98 ^b	0.0001
TC (mg dL ⁻¹)	40.32±1.41 ^b	32.77±3.12 ^c	61.83±2.25 ^a	42.92±3.95 ^b	0.0001
LDL (mg dL ⁻¹)	13.23±0.88 ^b	9.99±1.16 ^c	20.73±1.69 ^a	13.46±0.76 ^b	0.0001
HDL (mg dL ⁻¹)	20.15±1.61 ^c	25.13±1.19 ^b	30.46±1.55 ^a	26.55±1.87 ^b	0.0001
Day 30					
TG (mg dL ⁻¹)	63.03±1.64 ^b	31.40±1.80 ^d	87.78±2.58 ^a	57.93±2.97 ^b	0.0001
TC (mg dL ⁻¹)	103.82±7.20 ^b	95.6±4.36 ^c	150.23±2.44 ^a	120.39±14.10 ^b	0.0001
LDL (mg dL ⁻¹)	30.47±1.73 ^c	16.27±2.09 ^d	56.73±2.77 ^a	44.84±4.86 ^b	0.0001
HDL (mg dL ⁻¹)	57.55±1.91 ^a	60.75±4.82 ^a	58.09±1.36 ^a	56.56±1.85 ^a	0.0003
Day 90					
TG (mg dL ⁻¹)	89.46±1.93 ^b	60.89±2.12 ^d	133.72±3.49 ^a	79.67±1.78 ^c	0.0001
TC (mg dL ⁻¹)	121.42±5.92 ^b	104.91±10.76 ^c	160.53±2.62 ^a	137.63±18.33 ^a	0.0001
LDL (mg dL ⁻¹)	35.31±2.34 ^b	20.10±1.37 ^c	53.79±1.80 ^a	33.86±2.87 ^b	0.0001
HDL (mg dL ⁻¹)	62.12±1.99 ^a	53.36±2.11 ^b	41.16±2.23 ^c	58.42±1.33 ^a	0.0001

Note: TG = triglycerides, TC = total cholesterol, LDL-C = LDL cholesterol, HDL-C = HDL cholesterol. Values with different superscript letters (a, b, c, d) are significantly different ($p < 0.05$).

A cafeteria diet is frequently associated with alterations in the plasma oxidative stress in rodent models. In our study, the offspring of obese dams presented the elevated levels of plasma nitric oxide, superoxide anion and proteins carbonyl accompanied by attenuated antioxidant enzymes' activities remains to the adulthood in agreement with previous studies.²⁵

The high antioxidant capacity of olive oil, the main source of fat in the Mediterranean diet, has been attributed to its richness in phenolic compounds with high antioxidant capacity, e.g., hydroxytyrosol, tyrosol, oleuropein aglycon and its derivatives, and to the high proportion of monounsaturated fatty acids (MUFA), namely oleic acid, which are naturally found in extra virgin olive oil

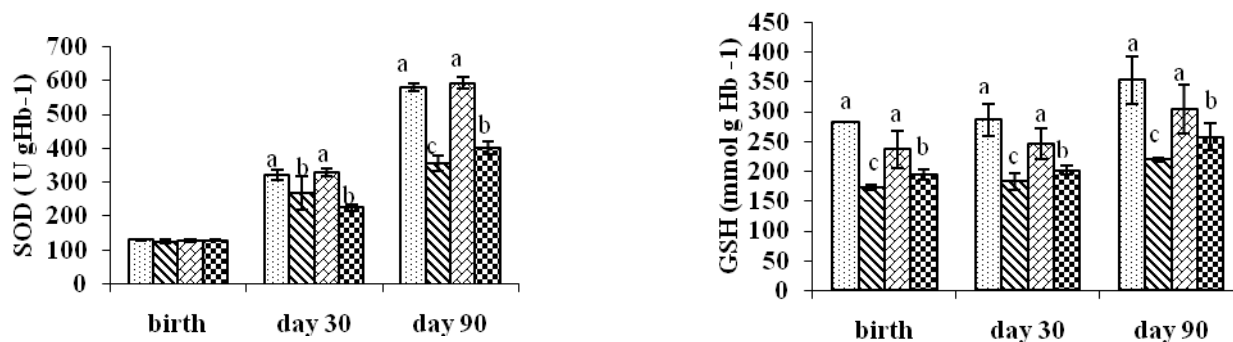


Figure 1. Erythrocyte antioxidant status in control and experimental rats. Values are presented as means \pm standard deviations (SD). SOD: superoxide dismutase, GSH: reduced glutathione. Values with different superscript letters (a, b, c, d) are significantly different ($p < 0.05$)

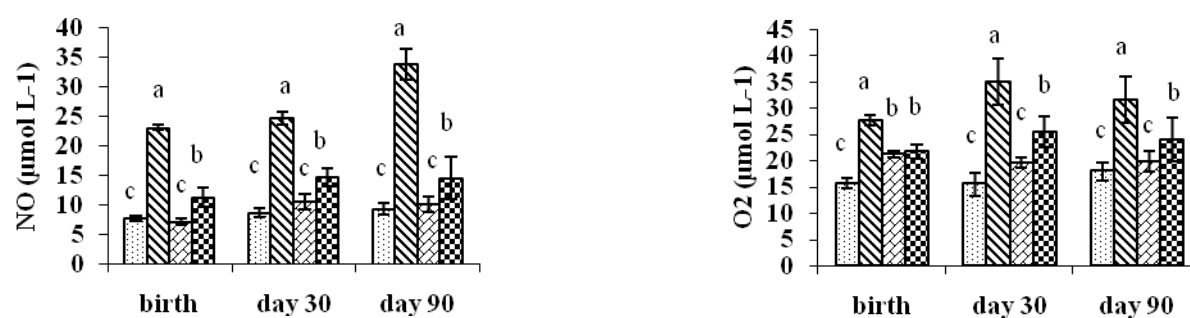


Figure 2. Plasma oxidant markers in control and experimental rats. NO = nitric oxide; O₂ = superoxide anion. Values with different superscript letters (a, b, c, d) are significantly different ($p < 0.05$).

Here, in an animal model of high-fat-diet-induced obesity, we show that maternal supplementation with olive oil at 5 % before gestation, during gestation and during lactation favorably affects body weight, biochemical parameters, lipid profile, and oxidant/antioxidant status in offspring at birth, on day 30 and on day 90.

In comparison to the control group, the obese (CAF) dams continued to get more body weight during gestation period, these may be related to increased fetal and placental weight, but supplementation of olive oil reduced gestational weight. These results may attribute to many factors, either the types of unsaturated fat (monounsaturated) or to the quantity of these fat in the diet or to the period of the experiment had an effect on the results. Our findings agreed with Sanaa Jameel Thamer et al study but they use olive oil 22.5 % after 12 weeks of high fat diet and before mating.¹⁵

Maternal olive oil supplementation results in a lower body weight of offspring at birth, but had no effects in obese offspring at weaning and at adulthood; however, under the challenge of a cafeteria diet, these animals show a greater increase in body weight and fat content. Animal studies have shown considerable disparity of this regard. In studies carried out in rats, a high fat maternal diet enriched in olive oil led to reduce postnatal weight gain in some studies, while other studies found no effect.^{26, 27}

Our data show that maternal dietary fatty acid balance does influence the development of the offspring. This becomes apparent in plasma glucose, urea, creatinine, uric acid and liver enzymes especially in cafeteria fed obese offspring, in agreement with previous reports,²⁸ but there is no effect on levels of ALP.

Laws *et al* using maternal diet supplementation with 10 % extra energy of olive oil (rich in MUFA) in the first half (G1) or second half of gestation, showed that MUFA supplementation during G1 reduced the incidence of low birth weight in piglets.²⁹

Furthermore, our study demonstrated that diet enriched with olive oil (5 %) considerably ameliorates lipid and lipoprotein disorders associated with higher HDL-cholesterol and lower LDL-cholesterol in offspring at birth and throughout adulthood. There is no significant difference in cholesterol values between CAFO and CAF at day 90 but remain within physiological limits.

Nitric oxide (NO) plays an important role in inflammatory process. Macrophages may greatly produce both levels of NO and superoxide, which rapidly react with each other to form peroxynitrite which oxidizes LDL, a key process in atherosclerosis. As it is recorded in our study, in obese offspring, maternal olive oil supplementation caused a reduction in plasma nitric oxide and superoxide anion with a concomitant increase in antioxidant enzyme activities.

We also observed a trend toward increase activity of glutathione reductase, which protects the mitochondrial inner membrane from oxidative stress damage. These findings are consistent with many studies that have shown that the antioxidant properties of olive oil are mainly due to its high content of polyphenolic compounds, which are strong antioxidants and radical scavengers.³⁰

Conclusion

Fetal programming has been a growing target of interest in scientific research, especially from the nutritional perspective. Our results clearly demonstrate that maternal intake of olive oil before gestation and during gestation display remarkable health benefits for the prevention of obesity and associated metabolic disorders by decreasing the lipoprotein metabolism and oxidant/antioxidant status alterations brought about by obesity in offspring at birth until adulthood.

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The authors declare that they have no conflicts of interest.

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