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ORIGINAL ARTICLE

# Oxidative Stress Biomarkers in Obese Mothers and Their Appropriate For Gestational Age Newborns

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## ABSTRACT

Obesity during pregnancy affects maternal and foetal lipid and lipoprotein levels, but our knowledge on oxidative stress biomarkers is limited. The aim of this study is todetermine the oxidant and antioxidant status in obese mothers and their newborns. 43 obese and 50 normal weight mothers and their appropriate for gestational age newborns were consecutively recruited from the maternity of Tlemcen hospital. The plasma total antioxidant activity (ORAC), vitamins A, C and E, hydroperoxides, carbonyl proteins and erythrocyte antioxidant enzyme activities (catalase, superoxide dismutase, glutathione reductase and peroxidase) were measured in mothers and their newborns. Changes in serum lipid and lipoprotein levels were also determined.

Obese mothers had low ORAC, vitamin C and E values, glutathione peroxidase and superoxide dismutase activities, high plasma triglycerides, hydroperoxide and carbonyl protein levels as compared to control mothers. Newborns of obese mothers also showed decreased ORAC, vitamins and increased hydroperoxides and antioxidant enzyme activities as compared to control newborns. There were no significant differences in plasma lipid and lipoprotein concentrations between newborns of obese mothers and those of control mothers. There were significant relationships between maternal and neonate oxidative stress biomarkers, thus, suggesting that maternal oxidant/antioxidant imbalance is an important causative factor in foetal stress in the obese group.

In conclusion, obese mothers and their newborns are exposed to oxidative stress. Their oxidant and antioxidant status should be carefully considered and appropriate management should be organized during the pregnancy and the early postnatal period, including antioxidant supplementation.

**Key Words:** obesity; pregnancy; oxidative stress; mothers; newborns; lipids.

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## Introduction

Obesity is one of the most common health problems in pregnant women. Maternal obesity is associated with several complications such as high blood pressure, eclampsia, gestational diabetes and macrosomia [1],[2],[3]. Obesity is associated with glucose and lipid metabolism abnormalities, increased cardiovascular risk and oxidative stress

[4],[5]. Obesity during pregnancy also affects maternal and foetal lipid and lipoprotein levels [6],7], but our knowledge on oxidative stress biomarkers is limited.

The steady-state formation of free radicals which are produced during cell metabolism is normally balanced by a similar rate of consumption by antioxidants. Under normal conditions, protective intracellular enzymes, mainly catalase, superoxide dismutase, glutathione peroxidase and reductase and non-enzymatic antioxidants such as glutathione, vitamin A, C and E prevent the accumulation of free radicals. Oxidative stress may result from imbalance in this pro-oxidant-antioxidant equilibrium. Oxidative stress has been implicated in several diseases such as atherosclerosis, diabetes and obesity [5],[8],[9],[10]. Obesity is an independent risk factor for a reduction in erythrocyte antioxidant enzyme activities and is associated with lower levels of serum antioxidants [11],[12]. Markers of lipid peroxidation as well as markers of protein oxidation were elevated in obesity [11],[13].

Pregnancy is a state of oxidative stress which is characterized by the placental production of reactive oxygen species (ROS) including superoxide ($O2^{-}$) and hydrogen peroxide (H2O2). In normal pregnancy, the rate of production of ROS is offset by their elimination by antioxidant defenses [14],[15]. However, in complicated pregnancies such as preeclampsia, pregnancy-induced hypertension and gestational diabetes mellitus, excessive ROS production overpowers antioxidant defenses, leading to an overall greater degree of oxidative stress [16],[17]. A significant correlation was found between some maternal and cord blood oxidative stress markers [18],[19], particularly in small for gestational age newborns [20],[21]. In the foetus, increased free radical production with concomitant upregulation of antioxidant reserve has been evidenced and oxidant/antioxidant balance is considered to be crucial during the foetal-to-neonatal transition [22]. Labour results in an increased radical activity in the foetus and the neonate and the delivery mode would affect maternal and foetal oxidant status [23],[24]. Since obese pregnant women have prolonged labour, maternal and foetal oxidative stress could be enhanced. Although different studies have shown that obesity is associated with increased oxidative stress and lipid peroxidation [9],[10],[11],[12],[13] and that maternal obesity during pregnancy is associated with metabolic alterations [6],[7], to the best of our knowledge, there are no reports in the literature on the effect of obesity on the maternal and foetal oxidant / antioxidant status.

The aim of the present study was to test the hypothesis that obesity increases oxidative stress in mothers and also in their newborns. Therefore, several markers of oxidative stress were assessed by measuring the overall capacity of plasma samples to scavenge oxygen radicals [ORAC (oxygen radical absorbance capacity)], the concentrations of plasma vitamins (A, C and E), hydroperoxides, carbonyl proteins, and the activities of erythrocyte SOD (superoxide dismutase), GSH-PX (glutathione peroxidase), GSSG-Red (glutathione reductase) and CAT (catalase) in obese mothers and their neonates. Changes in serum lipid and lipoprotein levels were also determined. The present study aimed to understand how obesity during pregnancy affects the maternal and foetal oxidant/antioxidant status.

## Material and Methods

### Patients

The study population included 50 normal weight and 43 obese women who gave birth at the Maternity department of Tlemcen Hospital, Tlemcen, Algeria. They were recruited successively from among the women who were admitted at the hospital. A written consent was obtained from all the subjects and the study was approved by the Tlemcen Hospital Committee for Research on Human Subjects. The women claimed to have no history of chronic diseases,

eclampsia, infections or foetal anomalies. All were tested for gestational diabetes according to the World Health Organization criteria and all had normal glucose tolerance test during the third trimester and within 48 hrs of delivery. Maternal obesity was quantified by prepregnancy body mass index (BMI, $Kg/m^2$). Obese pregnant patients were defined as having a BMI $\geq$ 30 $Kg/m^2$, whereas those with a BMI between 19 and 25 $Kg/m^2$ were considered to be normal weight control gravidas. Care was taken to ensure that all the subjects were of similar age, gestational age and parity. All these women had uncomplicated singleton pregnancies. None showed any abnormalities during labour and delivered vaginally at term. Gestational age was estimated by the last menstrual period and was confirmed by a first-trimester ultrasound scan. Newborn weight was recorded immediately after delivery. All newborns were appropriate for gestational age and AGA (birth weight between the 10th and 90th percentiles which corresponded to 2600 - 3900 g according to our population standard curves). Maternal and neonatal characteristics are shown in [Table1/Fig 1].

**(Table/Fig 1) Maternal And Neonate Characteristics.**

| Characteristics | Control | Obese |
|---|---|---|
| Number | 50 | 43 |
| Age (years) | 26 ± 1 | 27 ± 1.5 |
| BMI ($Kg/m^2$) | 22.80 ± 2.3 | 33.24 ± 1.7 † |
| Parity | 3 ± 1 | 2 ± 1 |
| Gestational age (weeks) | 38.40 ± 0.30 | 38.20 ± 0.40 |
| Birth weight (g) | 3340 ± 280 | 3495 ± 206 |
| 5 min Apgar score | 9.2 ± 0.3 | 8.7 ± 0.5 |
| M/F sex ratio | 28 / 22 | 21 / 22 |

**Values Are Means ± SD. BMI, Body Mass Index (Weight / $Height^2$); M / F, Males / Females.**
**Significant Differences Between Obese And Control Groups Are Indicated As : † P<0.01.**

## Blood Samples

Fasting maternal blood samples were obtained from the arm veins of the mothers. Cord blood samples were obtained from the umbilical vein immediately following delivery and after the cutting of the umbilical cord. Blood samples were collected in heparinized tubes, were centrifuged and plasma was separated for assessing lipids, lipoproteins, vitamins, total antioxidant capacity, hydroperoxides and carbonyl proteins. The remaining erythrocytes were washed three times in isotonic saline, were hemolysed by the addition of cold distilled water (1/4), stored in the refrigerator at 4 °C for 15 min and the cell debris was removed by centrifugation (2000 g x 15 min). The haemolysates were appraised for antioxidant enzyme activities.

## Chemical Analysis Lipoprotein and Lipid Determination

Plasma lipoprotein fractions (LDL, d<1.063; HDL, d<1.21 g. $mL^{-1}$) were separated by sequential ultracentrifugation in a Beckman ultracentrifuge (Model L5-65, 65 Ti rotor), using sodium bromide for density adjustment.

Plasma triglycerides and total cholesterol and LDL and HDL - cholesterol contents were determined by enzymatic methods (Kits Sigma Chemical Company, St Louis, MO, USA).

## Scavenging Capacity of Plasma

The oxygen radical absorbance capacity of plasma (ORAC) employs the oxidative loss of the intrinsic fluorescence of allophycocyanin (APC), as we have previously described [8]. APC fluorescence decay shows a lag or retardation in the presence of antioxidants, which is related to the antioxidant capacity of the sample. Trolox was used as a reference antioxidant for calculating the ORAC values, with one ORAC unit defined as the net protection area provided by 1 μM final concentration of trolox.

## Determination of Plasma Levels of Vitamin A, C and E

Plasma α-tocopherol (vitamin E) and retinol (vitamin A) were determined by reverse phase HPLC and were detected by a UV detector at 292 nm for vitamin E and at 325 nm for vitamin A. Vitamin C levels were determined in plasma by using the method of Roe and Kuether [25].

## Determinations of Erythrocyte Antioxidant Enzyme Activities

Catalase (CAT EC 1.11.1.6) activity was measured by spectrophotometric analysis of the rate of hydrogen peroxide decomposition at 240 nm [26]. Enzyme activity was expressed as U/g Hb.. Glutathione peroxidase (GSH-Px EC 1.11.1.9) was assessed by the Paglia and Valentine method [27] by using cumene hydroperoxide as the substrate. One unit of glutathione peroxidase activity is defined as the amount of enzyme which gives a 90% decrease in glutathione concentration per min at a 1 mM starting glutathione concentration. Glutathione reductase (GSSG-Red EC 1.6.4.2) activity was determined by measuring the rate of NADPH oxidation in the presence of oxidized glutathione [28]. The unit of enzyme activity was defined as the amount of enzyme which oxidized 1 mmol of NADPH per min. Superoxide dismutase (EC 1.15.1.1) activity was measured by the NADPH oxidation procedure [29] and was expressed as units of SOD per g Hb.

## Determination of Plasma Hydroperoxides

Hydroperoxides (markers of lipid peroxidation) were measured by the ferrous ion oxidation-xylenol orange assay (Fox2) in conjunction with a specific ROOH reductant, triphenylphosphine (TPP).

## Determination of Plasma Carbonyl Proteins

Plasma carbonyl proteins (markers of protein oxidation) were assayed by the 2,4-dinitrophenylhydrazine reaction.

## Statistical Analysis

The values of the biomarkers were obtained by calculating means ± SD. The statistical analysis of the data was carried out by using STATISTICA (version 4.1, Statsoft, Tulsa, OK). The significance of the differences between the two groups was determined by the student's t-test after analysis of variance. A value of $P<0.05$ was considered to be statistically significant. Linear regression analysis was used to determine correlation coefficients between the maternal and neonatal variables.

# Results

## Lipid and Lipoprotein Parameters

Plasma lipid and lipoprotein values in obese and normal weight control mothers and their newborns are presented in [Table/Fig 2]. Plasma triglyceride values were increased by 29% ($P<0.05$) in obese mothers as compared to control mothers. No significant differences in plasma cholesterol, LDL-cholesterol and HDL-cholesterol concentrations were found between the obese and control mothers. There were no significant differences in the plasma lipid and lipoprotein concentrations between the newborns of obese mothers and those of control mothers.

**(Table/Fig 2) Lipid And Lipoprotein Levels In Mothers And Their Newborns.**

| | Control | Obese |
|---|---|---|
| **Mothers** | | |
| Total cholesterol (mmol/L) | 6.48 ± 0.23 | 6.54 ± 0.20 |
| Triglycerides (mmol/L) | 2.31 ± 0.28 | 2.98 ± 0.21 * |
| HDL–C (mmol/L) | 1.62 ± 0.24 | 1.57 ± 0.30 |
| LDL–C (mmol/L) | 4.07 ± 0.22 | 4.29 ± 0.16 |
| **Newborns** | | |
| Total cholesterol (mmol/L) | 1.76 ± 0.21 | 1.84 ± 0.24 |
| Triglycerides (mmol/L) | 0.73 ± 0.18 | 0.95 ± 0.23 |
| HDL–C (mmol/L) | 0.92 ± 0.11 | 0.83 ± 0.09 |
| LDL–C (mmol/L) | 0.50 ± 0.08 | 0.54 ± 0.07 |

**Values Are Means ± SD. HDL-C, High Density Lipoprotein-Cholesterol; LDL-C, Low Density Lipoprotein-Cholesterol.**

**Significant Differences Between Obese And Control Groups Are Indicated As : * P<0.05.**

## Oxidative Stress Biomarkers

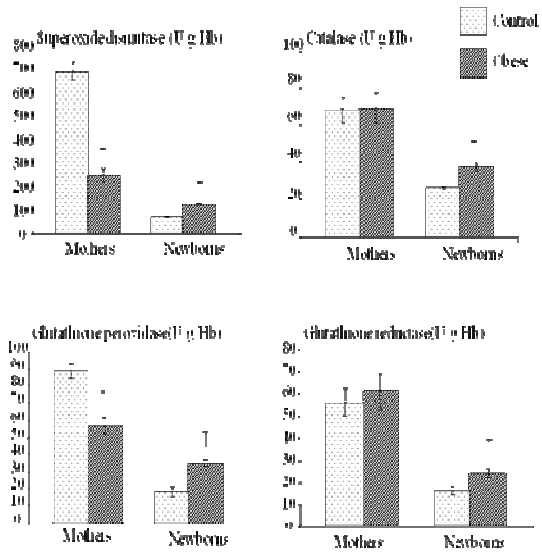
Oxidative stress biomarkers in mothers and neonates are shown in [Table/Fig 3] and [Table/Fig 4]. Plasma total antioxidant status (ORAC) was lower (- 29%, P<0.05) in obese mothers than in controls [Table/Fig 3](Table3). While plasma vitamin A levels did not differ significantly between the obese and control groups, vitamin C and E levels were significantly lower in obese mothers as compared to their controls (- 50% and – 39%, respectively, P<0.01). Plasma hydroperoxide and carbonyl protein levels were higher in obese mothers than in controls (+ 100% and + 73%, respectively, P<0.001). Variations in the biomarkers of oxidative stress which were observed in the newborns of obese mothers were parallel to those seen in their mothers, except for the carbonyl protein levels. In fact, ORAC, vitamin C and E levels were decreased (- 30%, P<0.05; - 50% and – 46%, P<0.01, respectively), while hydroperoxides were increased (+ 60%, P<0.01) in the newborns of obese mothers as compared to the control newborns. Vitamin A and carbonyl proteins did not differ between the two groups of newborns.

**(Table/Fig 3) Oxidative Stress Biomarkers In Mothers And Their Newborns.**

| | Control | Obese |
|---|---|---|
| **Mothers** | | |
| ORAC (Arbitrary Units) | 2.89 ± 0. 38 | 2.06 ± 0.17 * |
| Vitamin A (µmol/L) | 14.32 ± 2.16 | 12.79 ± 1.89 |
| Vitamin C (µmol/L) | 66 ± 8.12 | 33.16 ± 4.22 † |
| Vitamin E (µmol/L) | 30.05 ± 3.56 | 18.43 ± 1.62 † |
| Hydroperoxides (µmol/L) | 2.44 ± 0.43 | 4.87 ± 0.25 ‡ |
| Carbonyl proteins (nmol/mg protein) | 1.66 ± 0.28 | 2.87 ± 0.40 ‡ |
| **Newborns** | | |
| ORAC (Arbitrary Units) | 1.93 ± 0.26 | 1.32 ± 0.11 * |
| Vitamin A (µmol/L) | 5.25 ± 0.53 | 4.78 ± 0.46 |
| Vitamin C (µmol/L) | 43.24 ± 3.46 | 22.52 ± 1.02 † |
| Vitamin E (µmol/L) | 14.76 ± 1.11 | 7.79 ± 0.85 † |
| Hydroperoxides (µmol/L) | 1.89 ± 0.33 | 3.06 ± 0.28 * |
| Carbonyl proteins (nmol/mg protein) | 1.04 ± 0.21 | 1.23 ± 0.26 |

**Values Are Means ± SD. ORAC, Plasma Oxygen Radical Absorbance Capacity Was Determined As Described In Materials And Methods. Significant Differences Between Obese And Control Groups Are Indicated As : * P< 0.05; † P<0.01; ‡ P<0.001.**

**(Table/Fig 4)Erythrocyte Antioxidant Enzyme Activities In Mothers And Their Newborns.**




**Values Are Means ± SD. Significant Differences Between Obese And Control Groups Are Indicated As : * P< 0.05; † P<0.01.**

Erythrocyte superoxide dismutase (SOD) and glutathione peroxidase activities were found to be significantly decreased (- 64% and - 36%, P<0.01, respectively), while catalase and glutathione reductase activities were unchanged in obese mothers versus controls [Table/Fig 4]. In contrast, SOD, catalase, glutathione peroxidase and glutathione reductase activities were significantly higher in the newborns of obese mothers as compared to the control newborns (+ 34%, + 48%, + 52% and + 56%, P<0.01, respectively).

## Relationships between Maternal and Foetal Variables

In the control group, there were no significant associations between the maternal and foetal lipid and lipoprotein levels. In the obese group, there was a positive and significant correlation between the maternal and cord plasma triglyceride levels (r = 0.29, P<0.05).

With respect to the oxidative stress biomarkers, there were significant and

positive correlations between the maternal and neonatal plasma vitamin A, C and E concentrations in the control group ($r = 0.22$, $r = 0.31$ and $r = 0.30$, $P<0.05$, respectively). However, there was no relationship between the maternal and neonatal ORAC, hydroperoxides, carbonyl proteins and erythrocyte antioxidant enzyme activities in the control group. In the obese group, there were significant and positive correlations between the maternal and neonatal ORAC ($r = 0.33$, $P<0.05$), plasma vitamins A, C and E ($r = 0.25$, $r = 0.28$ and $r = 0.30$, $P<0.05$, respectively) and hydroperoxides ($r = 0.42$, $P<0.01$). Additionally, maternal SOD and glutathione peroxidase activities were negatively correlated to neonatal SOD and to the glutathione peroxidase activities in the obese group ($r = - 0.43$ and $r = - 0.46$, $P<0.01$, respectively).

## Discussion

This study provides evidence that obesity alters the oxidant / antioxidant status in mothers and their AGA newborns. Obese mothers had high serum triglyceride concentrations, while total cholesterol and LDL- and HDL- cholesterol values were unchanged when compared with normal weight values. Hypertriglyceridaemia is well known in obese subjects [4],[30] and can be accounted for by two mechanisms: enhanced hepatic VLDL and triglyceride production and reduced adipose tissue lipoprotein lipase activity which restrains VLDL removal from the circulation. In agreement with our findings, previous studies have shown that obese mothers with normal glucose tolerance during pregnancy, whose newborns were AGA, had hypertriglyceridaemia [6]. However, obese mothers with impaired glucose tolerance whose newborns were large for gestational age, had more altered lipid and lipoprotein profiles as compared to obese mothers with AGA newborns and to control women [6],[7],[31]. High LDL-C and low HDL-C levels are seen in obesity which is associated with the insulin resistance state [30]. It is well known that obese patients are heterogeneous and not all develop severe hyperlipidaemia. Insulin resistance is a key factor which is associated with clustering atherogenic abnormalities, which include a typical atherogenic dyslipidaemic state (high triglyceride and apolipoprotein B concentrations, increased LDL-cholesterol and a reduced concentration of HDL-cholesterol) [32]. Pregnancy also causes increments in both plasma and lipoprotein cholesterol and triglyceride levels [6],[33]. High serum oestrogen levels and increasing insulin resistance during gestation are considered to be responsible for this hyperlipidaemia [33],[34]. It has been shown that lipid and lipoprotein changes during pregnancy were similar in obese and non obese women [6]. In our study, hypertriglyceridaemia was accentuated in obese mothers and appeared to relate to the excess adipose tissue which exposes the liver to high concentrations of free fatty acids, leading to increased hepatic triglyceride production and secretion. Lipid and lipoprotein profiles were not significantly altered in AGA newborns of obese mothers, in agreement with previous studies [6]. Significant positive correlation was found between maternal and foetal plasma triglyceride levels in obese pregnancy, supporting the hypothesis that increased serum triglycerides may lead to an enhanced fatty acid transport through the placenta after placental lipoprotein lipase hydrolysis and may consequently increase supply to the foetal liver and enhance the foetal hepatic triglyceride synthesis. In our study, triglyceride levels in the newborns of obese mothers were higher than the control values, but the difference did not reach statistical significance.

Our data revealed that the total antioxidant activity (ORAC) was decreased in the plasma of obese mothers in favour of an oxidative stress in these women. The reduction of ORAC was associated with increased oxidative stress biomarkers such as hydroperoxide and protein carbonyl levels in obese mothers. Elevated levels of oxidant markers in these obese women could result from their abnormal metabolism and

metabolites in their adipose tissue and/or excessive proinflammatory and inflammatory cytokines release [4],[5],[10]. Protein carbonyl contents were found to be increased in overweight subjects [13] and they reflect the amount of oxidative stress which the person has been exposed to, during a long time period.

As far as the vitamins are concerned, we found no alterations in the levels of vitamin A, whereas the levels of vitamin C and E were lower in obese mothers than incontrols, in agreement with previous studies [35]. Low plasma levels of vitamin C and E could reflect their high utilisation rate, thus, suggesting that these vitamins may be used to reduce oxidative stress in obese mothers. It is well reported that oxidative stress is induced by both the increases in free radicals and by the disturbance of the free radical scavenging system in obesity. Alternatively, it is also possible that reduced vitamin C and E concentrations reflect low intake [36], which resulted in a decreased antioxidant defence system in obese mothers.

AGA newborns of obese mothers also showed low ORAC and high hydroperoxide levels as compared to the newborns of non obese mothers. As ORAC measures the global ability to resist oxidative stress and hydroperoxides reflect the effects of oxidative stress, resulting in tissue damage, high hydroperoxides and low ORAC values suggest that these infants are coping with oxidative stress early in life. Additionally, newborns of obese mothers had low plasma vitamin C and E levels, thus, reflecting low maternal concentrations. It is well known that foetal vitamins are delivered from the maternal circulation [36]. The increase in the plasma lipid peroxidation and protein oxidation in maternal obesity which is seen in the present study was associated with reduced erythrocyte antioxidant SOD and glutathione peroxidase activities in obese mothers. In contrast, catalase and glutathione reductase activities were unchanged by obesity in these mothers. Several investigators have reported contradictory findings regarding the antioxidant status in obesity [5],[9],[11],[17],[18]. A reduction in SOD, the primary enzyme that inactivates the superoxide radical and in the glutathione peroxidase activity which is involved in the detoxification of H2O2, would lead to increased numbers of free radicals and this could thereafter be responsible for the increased levels of hydroperoxide and carbonyl proteins in obese mothers. Antioxidant enzymes may also be consumed or inactivated in high oxidative conditions. In contrast to their mothers, newborns of obese mothers had enhanced SOD, catalase, glutathione peroxidase and glutathione reductase activities as compared to control newborns. The over expression of antioxidant activities in these infants might be an adaptive response with an induction to counter the effect of increased oxidative stress. In our study, higher levels of hydroperoxides and lower levels of ORAC, vitamin C and E in AGA infants of obese mothers, when compared with control newborns of normal weight mothers, suggested that these infants were exposed to greater oxidative stress despite higher antioxidant enzyme activities.

Our findings showed that newborn oxidant and antioxidant status in non obese pregnancy was not related to maternal status, except for vitamin A, C and E. However, in obese pregnancy, neonatal status was closely related to the maternal status, since there were significant and positive correlations between the maternal and neonatal ORAC, vitamins, hydroperoxides and there were negative correlations between the maternal and neonatal SOD and glutathione peroxidase activities. We provided novel evidence that maternal oxidant / antioxidant imbalance induced neonatal oxidative stress in obese pregnancy.

In conclusion, obesity increases oxidative stress in mothers and also in their AGA newborns.

We hypothesize that it would not be unreasonable to consider antioxidant supplements in early infancy for AGA newborns of obese mothers. Alternatively, obese mothers could be supplemented with additional antioxidant nutrients during pregnancy to enhance the endogenous ability of their newborns to resist oxidative stress.

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