RELATIONSHIP BETWEEN MATERNAL OBESITY AND INCREASED RISK OF PREECLAMPSIA.

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ABSTRACT

Introduction: *The incidence of obesity has risen over the past several decades and in spite of advancement in modern medicine, it remains a risk factor for maternal morbidity and mortality.*

Objective: *To determine the association between obesity (increased body mass index) and increased risk of preeclampsia.*

The possible role of serum leptin was also evaluated.

Methods: *250 pregnant women were included in this study. They were selected according to their BMI at 20 weeks of gestation and allocated into 5 study groups (each n= 50). At 20 weeks of gestation, BMI, mean arterial blood pressure was calculated. Proteinuria, serum uric acid and leptin were measured. At 28 weeks of gestation reevaluation of BMI, mean arterial blood pressure and serum uric acid were done. While serum leptin estimation was only reevaluated on the 37 weeks. Cases of preeclampsia were diagnosed and classified either mild or severe.*

Results: *It was found that preeclampsia was diagnosed in 20 cases. Among them 12 cases were diagnosed as mild preeclampsia in group A , 2 cases (4% of normal BMI) , 2 cases in group C (4% of obese class 1) , 6 cases in group D (12 % of obese class 11) and 2 cases in group E (4 % of obese class 111). Severe preeclampsia was diagnosed in 4 cases of group C (8 % of obese class 1) , 2 cases of group D (4% of obese class 11) and 2 cases of group E (4 % of obese class 111) .*

The relative risk of preeclampsia in cases of increased BMI was 2.25. The cases that developed preeclampsia had statistically significant elevated serum uric acid when compared to the normotensive cases at 28 and 37 weeks of gestation. Serum leptin level increased significantly with the increase in BMI and preeclamptic cases had statistically significant higher mean serum leptin at 28 and 37 weeks than normotensive cases.

Conclusion: *Maternal obesity is associated with a higher risk of adverse maternal and perinatal outcomes including preeclampsia.The dyslipidemia and the exaggerated inflammatory response associated with maternal obesity are thought to contribute to widespread endothelial dysfunction and the subsequent maternal syndrome in preeclampsia.*

Obesity is associated with higher mean serum leptin level. The levels of serum leptin are significantly higher in pre-eclampsia when compared to normotensive pregnant women and may contribute to endothelial dysfunction involved in the pathogenesis of preeclampsia.

Keywords: *preeclampsia –maternal obesity*

Abbreviation:

- **BMI:** Body mass index
- **VLDLs:** Very Low Density Lipoproteins
- **LDLs:** Low Density Lipoproteins

INTRODUCTION

Preeclampsia is a disease with worldwide significance to mothers and infants. Its greatest impact is in developing countries, where it accounts for 20-80% of the strikingly increased maternal mortality. However, even in developed countries there is a major effect, primarily on the fetus.[1]

Obesity is an excess of body fat which can be assessed by Body Mass Index (BMI). The incidence of obesity has risen over the past several decades and in spite of advancement in modern medicine, it remains a risk factor for maternal morbidity and mortality. Adipose tissue act as an endocrinal compartment so obesity is associated with endocrinal changes as increased basal insulin level with increased insulin resistance, increased free fatty acids, increased level of leptin, relative hyper-estrogenic state (gynoid type) and hyperandrogenemia (android type).[2]

It has become apparent that endothelial activation plays an integral role in preeclampsia.[3] Obesity is also associated with low-grade inflammation,[4] and these two conditions namely endothelial activation and low-grade inflammation may explain, at least partly, the association of obesity with preeclampsia. Moreover, obese pregnant women had significantly elevated levels of serum interleukin-6 and C-reactive protein as well as evidence of impaired endothelial function.[4]

The preeclampsia risk doubled with each 5 to 7 Kg/m² increase in maternal BMI. Accurately quantifying the relation between increased maternal body mass index and the risk of preeclampsia may better identify those at risk.[5]

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Essential hypertension is significantly correlated with weight, and severe obesity is thought to be associated with preeclampsia primarily because of confounding presence of essential hypertension.[6,7] Elevated BMI might contribute to preeclampsia through other mechanisms. Preeclampsia develops in two phases, the first of which is characterized by abnormal placentation with reduced placental blood supply. In the second phase, which is probably caused by oxidative stress, systemic maternal disease occurs.[8] Obesity is associated with dyslipidemia, such as an increase in plasma/serum triglycerides, VLDLs (very low density lipoproteins) and small dense low density particles, it is posited that small dense LDLs contribute to the generation of oxidative stress leading to endothelial cell dysfunction, a central pathophysiological feature of preeclampsia.[8,9]

Leptin is produced as a protein hormone by the adipocytes and its receptors are found in the brain, retina, liver and ovaries. It regulates feeding behavior, energy expenditure and reproductive functions. In the view that leptin's function is to resist obesity and promotes leanness led to the choice the name leptin from the Greek root leptos meaning thin. Recently leptin is considered as a novel placenta-derived hormone in human and may serve as a marker of preeclampsia, possibly reflecting placental hypoxia associated with severe preeclampsia.[10] Also it has been found that the maternal plasma leptin concentration is elevated before preeclampsia, suggesting that the increased expression of obesity related genes are involved in the pathogenesis of preeclampsia.[11]

The aim of this study was to determine the association between obesity (increased body mass index) and the risk of preeclampsia. The possible role of serum leptin was also evaluated.

METHODS

The study was conducted on 250 pregnant woman attended the out patient clinic of Shatby Maternity University Hospital at 20, 28 and 37weeks of gestation. Only primigravidae with singleton pregnancies were included with age ranging between 20 and 30 years They were selected according to their BMI at 20 weeks of gestation and allocated into the five study groups (each n=50):

Group A: normal (BMI 18.50-24.99).
Group B: preobese (BMI 25-29.99).
Group C: obese class I (BMI 30-34.99).
Group D: obese class II (BMI 35-39.99).
Group E: obese class III (BMI>40).

Exclusion criteria was chronic hypertension, diabetes mellitus, multiple gestations and renal diseases

After approval of the local ethics committee all pregnant women were briefed about the nature of the study and an informed consent was obtained from all of them before inclusion in the study.

All the studied women were subjected to the following:

At twenty week of gestation:

1. Complete history taking.
2. Clinical examination especially
- The BMI which is calculated as:

$$BMI=\frac{\text{weight (kg)}}{\text{height}^2(\text{m}^2)}$$

- The mean arterial blood pressure which is calculated as:

1/3puls pressure +diastolic blood pressure.

3. Obstetric ultrasound examination was done to confirm viability, gestational age and to exclude multiple gestation.
4. laboratory investigations:

- Dipstick urine analysis for proteinuria done by multistix URS 10 test strips.
- Serum uric acid was measured by enzymatic color test with Olympus OSR6098.
- Serum leptin was measured using DRGLeptin (sandwich) ELISA (EIA-2395) USA.

Follow-up visits:

At twenty eight weeks and thirty seven weeks of gestation the following parameters were re-evaluated

1- Body mass index (kg/m²).
2- Mean arterial blood pressure estimation.

If systolic BP is ≥ 140 mmHg or the diastolic BP is≥ 90 mmHg re-evaluation was done after 6 hours to confirm elevated blood pressure.

3- Serum uric acid estimation.
4- Serum leptin estimation was done only on the thirty seven weeks.

Cases of preeclampsia were diagnosed and classified either mild or severe.

Statistical analysis of the data:

Data were analyzed using SPSS software package version 15.0 (SPSS, Chicago, IL. USA). Quantitative data was expressed using range, mean and standard deviation while qualitative data was expressed in frequency and percent. Qualitative data was analyzed using Chi square test to compare the studied groups. Quantitative data was analyzed using F-test (ANOVA) to compare the different studied groups. P value was assumed to be significant at 0.05.

Cases of preeclamptic toxemia once diagnosed were submitted to management protocols adopted in Shatby Maternity University Hospital.

RESULTS

The study was conducted on 250 pregnant women all of them were primigravidae. According to the selection criteria of their body mass index at the 20th week of gestation they were allocated into the five

study groups (each n=50).

Patient characteristics:

Maternal age: Table I:

The maternal age of the studied cases ranged between 20 and 30 years.

In group A the age ranged from 22 to 28 years with a mean 24.96 ± 1.74 years.

In group B the age ranged from 20 to 30 years with a mean 24.24 ± 2.96 years.

In group C the age ranged from 20 to 29 years with a mean 23.90 ± 2.91 years.

In group D the age ranged from 20 to 29 years with a mean 25.20 ± 2.78 years.

In group E the age ranged from 21.50 to 29 years with a mean 24.94 ± 2.27years.

The difference between the five studied groups was statistically insignificant.

Body mass index (BMI kg/m^2): Table II, Fig. 1:

According to the selection criteria, the cases were allocated into the 5 study groups (each n=50) according to their BMI on admission at the 20th week of gestation.

Group A had a normal BMI with a mean 24.48 ± 3.15kg/m^2.

Group B (the overweight) had a mean BMI 27.59 ± 0.77kg/m^2.

Group C (obese class I) had a mean BMI 33.14 ± 1.20kg/m^2.

Group D (obese class II) had a mean BMI 37.58 ± 1.18kg/m^2.

Group E (obese class III) had a mean BMI 43.20 ± 1.75kg/m^2.

The difference between the five studied groups was statistically significant ($p \leq 0.05$).

Mean arterial blood pressure: Table III, Fig 2:

There was no significant difference between the 5 studied groups as regard the mean arterial blood pressure at the 20th week of gestation.

At the 28th week the study groups did not show statistically significant differences as regard their mean arterial blood pressure. However, elevation of the mean arterial blood pressure was detected in 20 cases in group A (normal BMI), group C (obese class I), group D (obese class II), and group E (obese class III).

At the 37th week the study groups did not show statistically significant differences as regard their mean arterial blood pressure. However the 20 cases that showed elevation of mean arterial blood pressure during the 28th week were normotensive under Aldomet treatment.

Laboratory investigations:

1-Proteinuria: Table IV, Fig.3:

No significant proteinuria (2+ on dipstick examination or >300mg/24hours urine collection) was detected among the studied groups during the 20th week of gestation, while on the 28th week there was significant difference of proteinuria among the studied groups which was continued till the 37th week of gestation.

Comparison between the different studied groups (each n=50) according to incidence of preeclampsia (mild or severe) at 28 week: Table V, Fig. 4:

According to the previous data collected from the mean arterial blood pressure and the significant proteinuria 20 cases developed preeclampsia in this study. Among these 20 cases, 12 cases were classified as mild preeclampsia and 8 cases were classified as severe preeclampsia.

Mild preeclampsia developed in 2 pregnant woman in group A (4% of normal BMI), 2 pregnant woman in group C (4% of the obese class 1), 6 cases developed in group D(12% of the obese class II) and 2 case developed in group E(4% of the obese class III).

Severe preeclampsia was diagnosed in 4 cases of group C (8% of obese class 1), in 2 case (4% of obese class II) and in 2 case of group E (4% of obese class III).

There was significant difference in incidence of preeclampsia among the studied groups as shown in table V.

The relative risk (R.R) of preeclampsia in the cases of increased BMI: Table VI:

When we considered the studied cases as two groups, normal group (BMI 18.5-24.9 kg/m^2)and group with increased BMI (≥25kg/m^2), we found that incidence of preeclampsia in cases with increased BMI was 9%. While the incidence of preeclampsia in the cases of normal BMI was 4% R.R. = incidence of preeclampsia in cases with increased BMI 9% / incidence of preeclampsia in the cases of normal BMI 4%=2.25

2-Serum uric acid (mg/dl): Table VII, Fig.5:

There were no statistically significant differences between the five studied groups as regard the serum uric acid concentrations at the 20, 28 and 37week, only slight elevation was noticed on the 37th week in all the studied groups but it was statistically non significant.

Comparison between the normotensive cases (n=230) and the cases who developed preeclampsia (n=20) as regard the mean serum uric acid concentration (mg/dl): Table VIII, Fig 6:

The cases that developed preeclampsia either mild or severe had a statistically significant elevated serum uric acid ($p \leq 0.05$) when compared with the normotensive cases at the 28th and 37th weeks.

The serum uric acid level did not show a

statistically significant difference between the mild preeclampsia and the severe preeclampsia during the 28th week (p>0.05).

While during the 37th week the severe preeclamptic cases had a statistically significant elevated serum uric acid level than the mild preeclamptic cases (p≤0.05).

3- Serum leptin (ng/ml): Table IX, Fig.7:

Serum leptin mean level increased significantly with the increase in the body mass index when measured at the 20th week and the 37th weeks of gestation so the difference between the five study groups was statistically significant as regard the mean serum leptin (p≤0.05).

Comparison between the normotensive cases and the preeclamptic cases (mild and severe) as regard the level of mean serum leptin (ng/ml): Table X, Fig. 8:

At the 20th week of gestation:

The mean serum leptin was 43.01 ± 20.35ng/ml in the normotensive cases, while the mean serum leptin in the cases that developed mild preeclampsia later at the 28th week was 70.17 ± 13.54ng/ml and in the cases that developed severe preeclampsia later at the 28th week was 79.25 ± 8.53ng/ml.

The preeclamptic cases (mild and severe) had a statistically significant higher mean serum leptin (p≤0.05) than the normotensive cases.

At the 37th week of gestation:

The mean serum leptin was 63.80 ± 24.78ng/ml in the normotensive cases, while in the mild preeclampsia was 93.17 ± 20.24ng/ml and in the severe preeclampsia was 113.88 ± 10.30ng/ml.

Mean serum leptin was statistically significant higher in the preeclamptic cases than in the normotensive cases (p≤0.05).

However, there was no statistically significant difference between the mild and the severe preeclamptic cases as regard the mean serum leptin.

Table I: Comparison between the different studied groups (each n=50) according to maternal age (years)

	Normal (Group A) n=50	Over weight (Group B) n=50	Obese class I (Group C) n=50	Obese class II (Group D) n=50	Obese class III (Group E) n=50
Age(years)					
Range	22.00 – 28.00	20.00 – 30.00	20.00 – 29.00	20.00 – 29.00	21.50 – 29.00
Mean ± SD	24.96 ± 1.74	24.24 ± 2.96	23.90 ± 2.91	25.20 ± 2.78	24.94 ± 2.27
F (p)	1.142 (0.340)				

F: F test (ANOVA) *: Statistically significant at p ≤ 0.05

Table II: Comparison between the different studied groups (each n =50) according to the mean body mass index (BMI kg/m^2) at 20 week.

BMI (kg/m^2) at 20 week	Normal (Group A) n=50	Overweight (Group B) n=50	Obese class I (Group C) n=50	Obese class II (Group D) n=50	Obese class III (Group E) n=50
Mean±SD	24.48 ± 3.15	27.59 ± 0.77	33.14 ± 1.20	37.58 ± 1.18	43.20 ± 1.75
F (p)	860.471* (<0.001)				
Sig. with	B, C, D, E	A, C, D, E	A, B, D, E	A, B, C, E	A, B, C, D

F: F test (ANOVA) *: Statistically significant at p ≤ 0.05

Table III: Comparison between the different studied groups (each n=50) according to the mean arterial blood pressure (mmHg).

Mean arterial blood pressure(mmHg)	Group A n=50	Group B n=50	Group C n=50	Group D n=50	Group E n=50
20 week Mean±SD	82.84 ± 8.90	80.31 ± 13.25	84.10 ± 9.12	82.37 ± 10.16	85.50 ± 9.66
F (p)	1.219 (0.303)				
28 week Mean±SD	83.64 ± 8.57	83.38 ± 8.20	87.04 ± 15.90	87.77 ± 15.34	86.90 ± 13.18
F (p)	2.032 (0.091)				
37 week Mean±SD	83.04 ± 8.99	82.24 ± 9.02	84.37 ± 10.86	85.37 ± 10.07	83.77 ± 8.22
F (p)	1.316 (0.265)				

F: F test (ANOVA) *: Statistically significant at p ≤ 0.05

Table IV: Comparison between the different studied groups (each n= 50) According to proteinuria

Proteinuria(>2+ on dipstick)	Group A n=50		Group B n=50		Group C n=50		Group D n=50		Group E n=50	
	n	%	n	%	n	%	n	%	n	%
28 week										
Absent	48	96.0	50	100.0	44	88.0	42	84.0	46	92.0
Present	2	4.0	0	0.0	6	12.0	8	16.0	4	8.0
χ^2 (p)	10.870* (0.028)									
Significant with#	D		C,D,E		B		A,B		B	
37 week										
Absent	48	96.0	50	100.0	44	88.0	42	84.0	46	92.0
Present	2	4.0	0	0.0	6	12.0	8	16.0	4	8.0
χ^2 (p)	10.870* (0.028)									
Significant with#	D		C,D,E		B		A,B		B	

χ^2: Chi square test
: Using significance from chi-square test between each two groups
*: Statistically significant at $p \leq 0.05$

Table V: Comparison between the different studied groups (each n=25) according to the incidence of preeclampsia at 28 week

	Group A n=50		Group B n=50		Group C n=50		Group D n=50		Group E n=50	
	n	%	n	%	n	%	n	%	n	%
Normotensive cases	48	96.0	50	100.0	44	88.0	42	84.0	46	92.0
Preeclampsia	2	4.0	0	0.0	6	12.0	8	16.0	4	8.0
χ^2(p)	10.870* (0.028)									

χ^2: Chi square test
#: Using significance from chi-square test between each two groups
*: Statistically significant at $p \leq 0.05$

Table VI: The incidence of preeclampsia in the cases of increased BMI

	Normal BMI n = 50	Increased BMI n = 200
Normotensive cases	48	182
Preeclampsia cases	2	18
Specific incidence	4%	9%

Table VII: Comparison between the different studied groups (each n=50) according to the mean serum uric acid level (mg/dl).

Uric acid(mg/dl)	Group A n=50	Group B n=50	Group C n=50	Group D n=50	Group E n=50
20 week Mean ± SD	2.60 ± 0.33	2.67 ± 0.30	2.63 ± 0.31	2.63 ± 0.34	2.73 ± 0.38
F (p)	1.219 (0.303)				
Sig. with	No sig.	No sig.	No sig.	No sig.	No sig.
28 week Mean ± SD	2.77 ± 0.58	2.74 ± 0.28	3.15 ± 0.98	3.01 ± 1.19	2.93 ± 0.90
F (p)	2.032 (0.091)				
Sig. with	No sig.	No sig.	No sig.	No sig.	No sig.
37 week Mean ± SD	3.76 ± 0.61	3.76 ± 0.33	4.11 ± 1.23	3.88 ± 1.20	4.00 ± 0.97
F (p)	1.316 (0.265)				
Sig. with	No sig.	No sig.	No sig.	No sig.	No sig.

F: F test (ANOVA)
*: Statistically significant at $p \leq 0.05$

Table VIII: Comparison between the normotensive cases (n=230) and the cases who developed preeclampsia (n=20) as regard the mean serum uric acid concentration (mg/dl):

Serum uric acid (mg/dl)	Normotensive n=230	Mild preeclampsia n=12	Severe preeclampsia n=8
28th week			
Range	2.00-6.80	3.00-7.30	3.10-6.80
Mean ± SD	2.72 ± 0.45	5.08 ± 0.98	5.41 ± 1.19
F (p)		209.932* (<0.001)	
p_1		<0.001*	<0.001*
p_2			0.158 (No sig.)
37th week			
Range	2.50-7.60	4.30-6.80	6.20-7.60
Mean ± SD	3.68 ± 0.55	5.98 ± 0.82	7.05 ± 0.45
F (p)		228.175* (<0.001)	
p_1		<0.001*	<0.001*
p_2			<0.001*

F: F test (ANOVA)
*: Statistically significant at $p \leq 0.05$
P1: value for LSD test for comparison between normotensive cases and (mild and severe preeclampsia).
P2: value for LSD test for comparison between mild and severe preeclampsia.

Table IX: Comparison between the different studied groups (each n=50) according to the mean serum leptin level (ng/ml)

Serum leptin (ng/ml)	Group A n=50	Group B n=50	Group C n=50	Group D n=50	Group E n=50
20 week	28.08	35.36	48.18	53.37	62.40
Mean±SD	± 9.46	± 7.81	± 25.60	± 19.16	± 20.04
F (p)			30.208* (<0.001)		
Sig. with	B, C, D, E	A, C, D, E	A, B, E	A, B, E	A, B, C, D
37 week	42.58	58.92	68.48	74.32	89.74
Mean±SD	± 13.65	± 17.53	± 26.07	± 26.14	± 20.85
F (p)			33.662* (<0.001)		
Sig. with	B, C, D, E	A, C, D, E	A, B, E	A, B, E	A, B, C, D

F: F test (ANOVA)
*: Statistically significant at $p \leq 0.05$

Table X: Comparison between the normotensive cases and the preeclamptic cases (mild and severe) as regard the mean serum leptin level (ng/ml) at 20 and 37 weeks

Serum leptin (ng/ml)	Normotensive cases n= 230	Mild preeclampsia n= 12	Severe preeclampsia n= 8
20 week			
Range	16.00-110.00	40.00-84.00	65.00-92.00
Mean ± SD	43.01 ± 20.35	70.17 ± 13.54	79.25 ± 8.53
F (p)		22.624* (<0.001)	
p_1		<0.001*	<0.001*
p_2			0.317 (No sig.)
37 week			
Range	19.00-124.00	60.00-120.00	100.00-125.00
Mean ± SD	63.80 ± 24.78	93.17 ± 20.24	113.88 ± 10.30
F (p)		23.831* (<0.001)	
p_1		<0.001*	<0.001*
p_2			0.063(No sig.)

F: F test (ANOVA)
*: Statistically significant at $p \leq 0.05$
P1: value for LSD test for comparison between normotensive cases and preeclamptic cases (mild and severe)
.P2: value for LSD test for comparison between mild and severe preeclampsia.

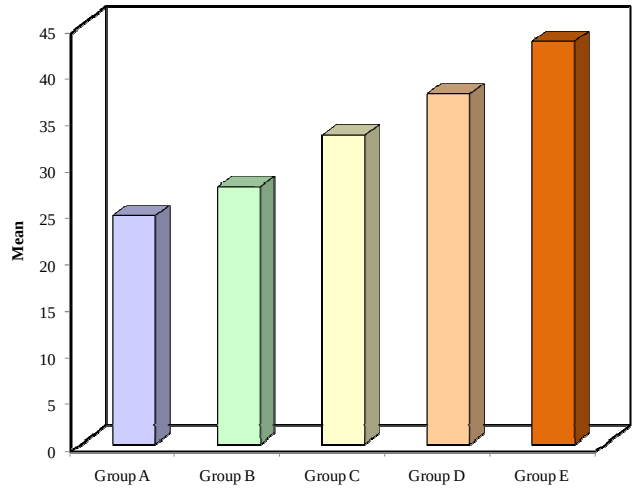

Fig 1: Comparison between the different studied groups (each n =50) according to the mean body mass index (BMI kg/m^2) at 20 week.

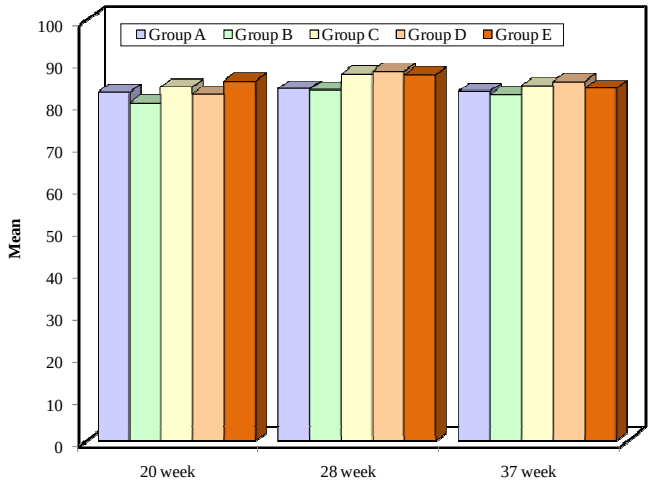

Fig 2: Comparison between the different studied groups (each n=50) according to the mean arterial blood pressure (mmHg).

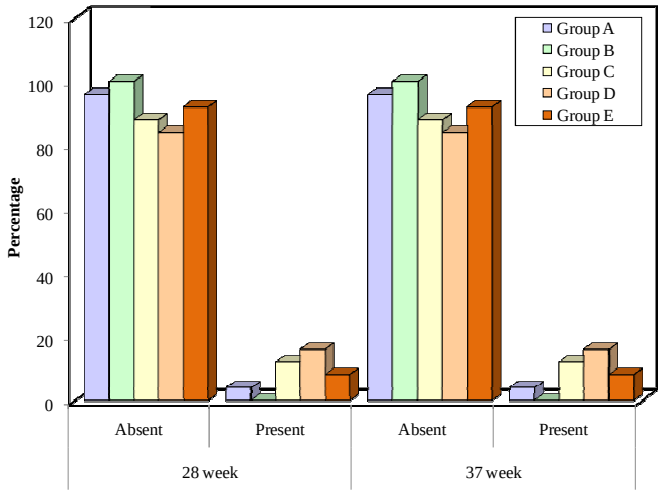

Fig 3: Comparison between the different studied groups (each n= 50) according to proteinuria

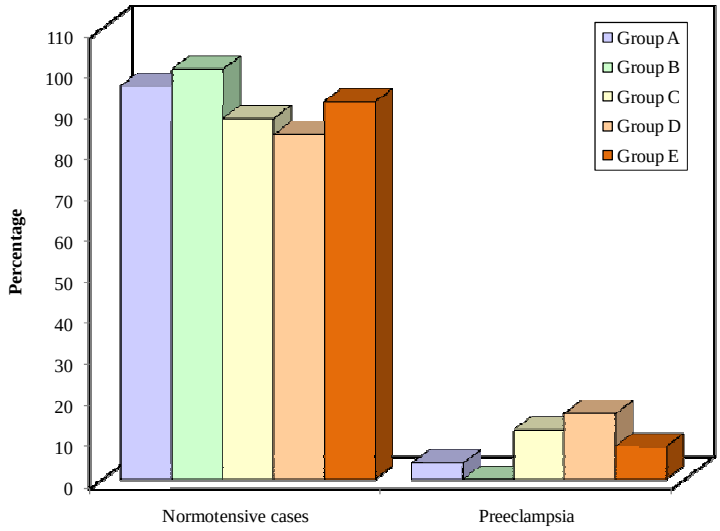

Fig 4: Comparison between the different studied groups (each n=50) according to the incidence of preeclampsia (mild or severe) at 28 week

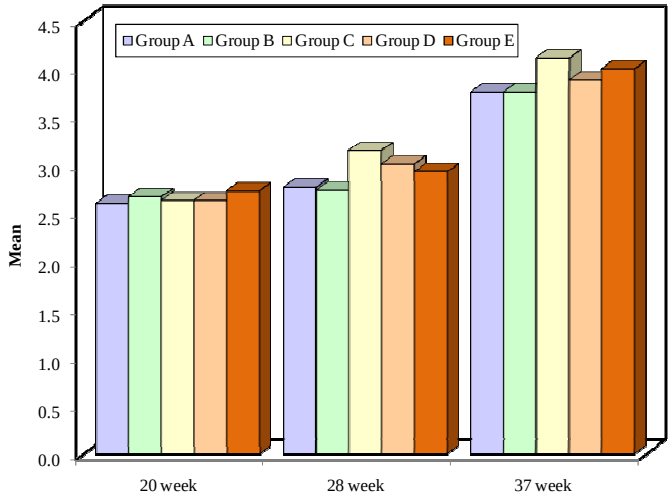

Fig 5: Comparison between the different studied groups (each n=50) according to the mean serum uric acid level (mg/dl)

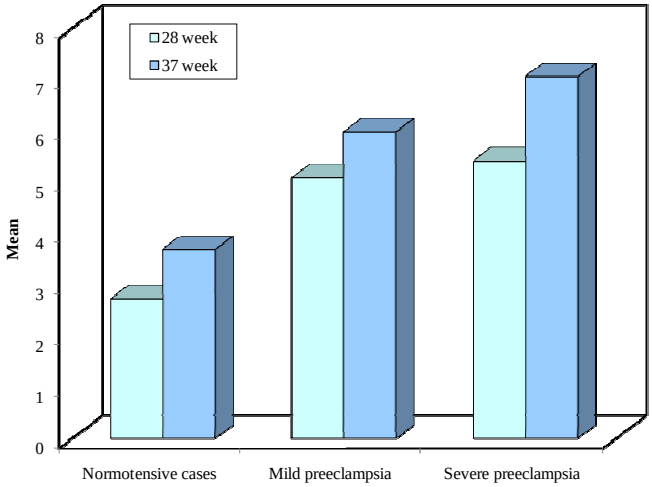

Fig 6: Comparison between the normotensive cases (n=230) and the cases who developed preeclampsia (n=20) as regard the mean serum uric acid concentration (mg/dl)

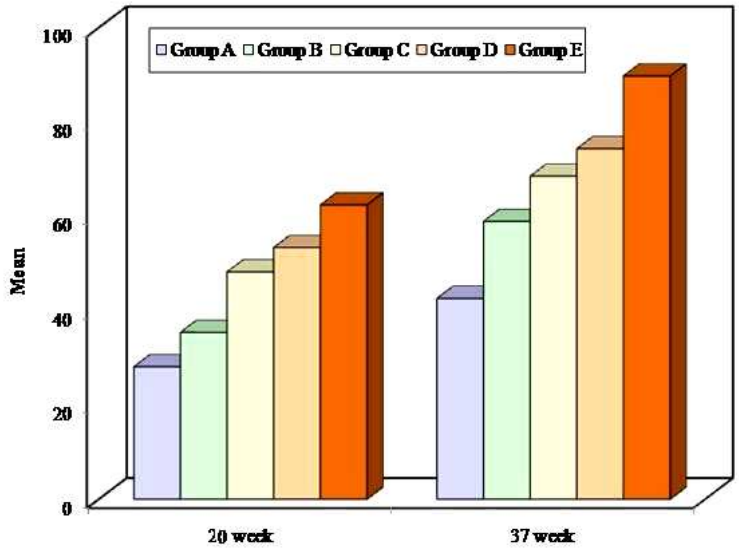

Fig 7: Comparison between the different studied groups (each n=50) according to the mean serum leptin level (ng/ml)

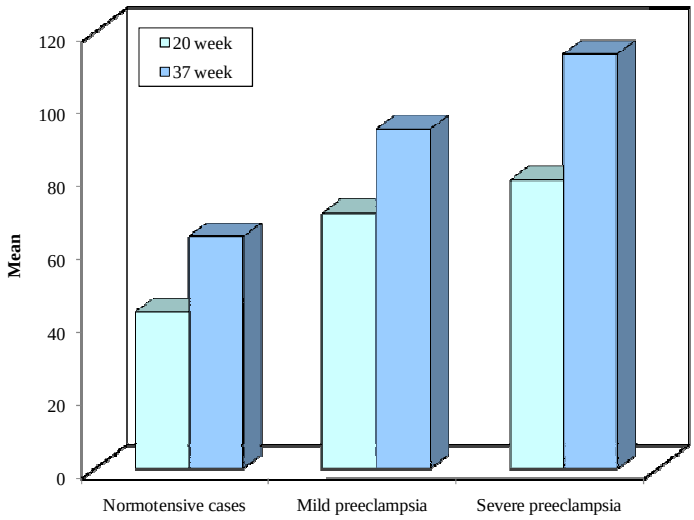

Fig 8: Comparison between the normotensive cases and the preeclamptic (mild and severe) as regard the mean serum leptin level (ng/ml) at 20 and 37 weeks

DISCUSSION

Preeclampsia is a multisystemic disorder peculiar to pregnancy after 20 weeks of gestation. It is characterized by widespread endothelial dysfunction throughout the maternal circulation resulting in hypertension attributable to vasoconstriction and significant proteinuria attributable to glomerular damage. It is established that there can be many different causes for the syndrome.[13]

Maternal obesity is associated with a higher risk of adverse maternal and perinatal outcomes. It is a validated risk factor for preeclampsia, but the mechanism of how it imparts increased risk is not completely understood.[14]

Obesity might act through its association with dyslipidemia[15] which results in an atherosclerotic-like lesion of spiral arterioles of the placenta, characterized by foam cell invasion and intravascular fibrin deposition leading to endothelial cell dysfunction.[16,17,18] Obesity also might acts through inflammatory mechanisms,[19] enhanced sympathetic adrenergic activity,[20-24] insulin resistance.[25] and chronic oxidative stress.[26]

The present study evaluated the relationship between maternal obesity and the risk of preeclampsia.The possible role of serum leptin was also evaluated. We studied 250 pregnant women at the 20, 28 and 37 weeks of gestation. They were selected according to their BMI to be categorized into the five studied groups (each n=50); normal (group A), overweight (group B), obese class I (group C), obese class II (group D) and obese class III (group E).

We found in the present study that preeclampsia was diagnosed in 20 cases (8%of cases). Among these 20 cases, 12 cases were classified as mild preeclampsia and 8 cases were classified as severe preeclampsia. Mild preeclampsia developed in 2 pregnant woman in group A (4% of normal BMI), in 2 cases in group C (4% of obese class 1) ,6 cases in group D (12% of the obese class 11) and 2 cases in group E (4% of the obese class 111).Severe preeclampsia was diagnosed in 4 cases of group C (8% of obese class 1), in 2 cases of group D (4% of obese class 11) and in 2 case of group E (4% of obese class 111).

It has been evident in the present study that increased BMI was associated with increased incidence of preeclampsia (9% of cases) while the incidence of preeclampsia in the cases of normal BMI was 4% and the relative risk of preeclampsia in the cases of increased BMI was 2.25. However we found that not all the obese pregnant women developed preeclampsia which means that there are unknown factors that manipulate the internal milieu of the pregnant females so they interact with the stressful situation in a manner that prevent the development of preeclampsia and if it develops it is either mild or severe. Most probably these factors are the power of the mother to clear free oxygen radicals or the antioxidant capacity of her body.

Lifestyle factors such as inadequate dietary intake of antioxidants, calcium and vitamins (especially vitamin E)[27] or physical inactivity during pregnancy may contribute to the association of obesity and preeclampsia as well, either through the metabolic disturbances (i.e., by increasing oxidative stress) or through the other mechanisms that had been described.

Lisa et al,[28] in their case-control study of 55 preeclamptic women and 165 pregnant controls at 20 weeks reported that increases in body mass index were associated with 1.7-fold increases in preeclampsia risk. While in our study the risk was 2.25.

Bodnar et al,[29] in their prospective study demonstrated that the risk of preeclampsia rose strikingly from a prepregnancy BMI of 15 kg/m^2 to a BMI of 35 kg/m^2.The risk of preeclampsia was approximately doubled at a BMI of 26 kg/m^2, tripled at a BMI of 30 kg/m^2, and halved at a BMI of 18 kg/m^2.

Brigitte L. et al 2006,[30] in their retrospective study, reported that the increase in BMI was associated with an increase in the development of preeclampsia as the overweight women (BMI ≥25 and <30 kg/m^2) had a 2-fold risk and the obese women (BMI ≥30 kg/m^2) had a 3.2-fold risk of developing pre-eclampsia when compared with women of normal weight (BMI ≥15.5 and <25 kg/m^2

O'Brien TE et al 2003,[2] in their study suggested that the risk of preeclampsia doubled with each 5-7 kg/m^2 increase in prepregnancy body mass index

Cedergren et al,[31] in their prospective population-based cohort study reported that the morbidly obese mothers when compared to the normal-weight mothers had an increased risk of preeclampsia and the associations were similar for women with BMI between 35.1and 40 but to a lesser degree.

Leptin is a non-glycosylated polypeptide product of obese (Ob) gene.[32] It is expressed predominantly by adipocytes, and smaller amounts of leptin are also secreted by cells in the epithelium of the stomach and in the placenta.[33]It acts in the hypothalamus to regulate appetite, energy expenditure and sympathetic nervous system outflow.[34] It seems likely that the placenta plays a role in increasing the maternal plasma leptin concentrations during normal or complicated pregnancies.[35]

The present study demonstrated that mean serum leptin level increased significantly with the increase in the body mass index when measured at the 20th week and the 37th weeks of gestation as it had statistically significant differences between the 5 studied groups ($p \leq 0.05$). Zimmet et al,[36] in their cross sectional study, found that leptin concentrations increased with the increase in body mass index which is in agreement with the present study. They found also that leptin concentrations were higher in women than men even at the same body mass index and were also strongly correlated with serum insulin concentrations even after adjusting for obesity in both sexes. So they reported that leptin may simply reflect the size of adipose tissue stores and the independent association with insulin concentration suggests a possible role in insulin resistance or hyperinsulinaemia.

The present study demonstrated also that the preeclamptic cases either mild or severe that were diagnosed at 28 weeks had a statistically significant higher mean serum leptin level ($p \leq 0.05$) than the normotensive cases when evaluated at 20 weeks and at 37 weeks. However, there was no statistically significant difference between the mild and the severe preeclampsia cases as regard the mean serum leptin level at 20 or 37 weeks ($p=0.317$, $p=0.063$) respectively.

Iftikhar et al[37] conducted a comparative cross-sectional study on 45 primigravidae with normal pregnancy and 45 primigravidae with preeclamptic pregnancy in their third trimester. The serum leptin levels were found to be elevated in pre-eclamptic group as compared to normal pregnancy which is in agreement with the results of our study. They found that serum leptin levels were higher in the severe group versus the mild group. This is in contradiction with the present study as there was no statistically significant difference between the mild and the

severe preeclamptic cases as regard the mean serum leptin level at 20 or 37 weeks. Their study did not include the effect of obesity in contrary to the present study whereas obesity was the main issue. Obesity can manipulate serum leptin level to a variable degree.[38] Rivera et al[39] evaluated plasma leptin level in 40 preeclampsia cases and 39 controls and they found that leptin concentrations were higher in the preeclamptic cases than in the controls (53.1±4.7 vs. 17.7±2.4 ng/ml, $p<0.05$) which is in agreement with the present study. Elevated leptin (≥ 14.5 ng/ml) was associated with a 3.8-fold increased risk of preeclampsia.

Michael et al[40] found that leptin is significantly increased in preeclampsia cases by univariat analysis but when using multivariat analysis of BMI, estrogen and sex hormone binding globulin they found that leptin did not add to the prediction of the severity of preeclampsia due to the confounding effect of the altered BMI, estrogen and sex hormone binding globulin. So they could not prove or disprove a causal relationship between leptin and the severity of preeclampsia .This in agreement with our results that leptin did not differ in the mild versus the severe preeclampsia cases due to the confounding effect of obesity on serum leptin level of the preeclampsia cases. There could be several possible causes for elevated leptin levels in preeclampsia. Impaired renal function is a pathophysiological component of preeclampsia and the measured increase in plasma leptin concentration may reflect reduced renal clearance. Also high leptin levels may be due to the possible haemo-concentration in preeclampsia caused by association of preeclampsia with reduced plasma volume.[39] Several studies suggested that BMI was responsible for the increase in leptin levels in preeclamptic women via increased leptin resistance. Moreover adipose tissue is a source of leptin. However, in pregnancy the body mass index does not only reflect adipose tissue mass because the fetus, the placenta, the amniotic fluid, increased plasma volume and extra vascular fluid accumulation all increases the maternal weight.[41] Placental ischemia may also explain the rapid increase in leptin concentration during late third trimester in PE as the placental hypo perfusion produces local hypoxia which consequently augments leptin gene expression in the placenta.[42] Also there is evidence that inflammatory mediators increase plasma leptin concentration and in preeclampsia circulating concentrations of the inflammatory cytokines such as tumor necrosis factor-α and interleukin -6 are increased.[43] Thus, there are several possible explanations for the higher leptin concentrations in pregnancies complicated by preeclampsia but the exact mechanism awaits further clarification.

Conclusion

From this work it was possible to reach the following conclusions:

Maternal obesity is associated with a higher risk of adverse maternal and perinatal outcomes including preeclampsia.The dyslipidemia and the exaggerated inflammatory response associated with maternal obesity are thought to contribute to widespread endothelial dysfunction and the subsequent maternal syndrome in preeclampsia. Obesity is associated with higher mean serum leptin level. The levels of serum leptin are significantly higher in pre-eclampsia when compared to normotensive pregnant women and may contribute to endothelial dysfunction involved in the pathogenesis of preeclampsia.

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