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Original research article

Antepartum and postpartum changes in adipokines, endothelial dysfunction, inflammatory markers and other biochemical parameters in preeclamptic women: A prospective observational cohort study

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Abstract
This study aimed at evaluating the role played by insulin resistance, lipid metabolism disorder, oxidative stress, resistin, vaspin, Interleukin-18 and asymmetric dimethyl arginine as a marker for endothelial dysfunction in the pathogenesis of preeclampsia.

This prospective observational cohort study involved 60 women who were classified into: 20 non-pregnant women (group 1 or control group), 20 normally pregnant women (group 2) and 20 preeclamptic women (group 3) at their third trimester.

The pregnant women were assessed at their third trimester and further re-evaluated four weeks after delivery. The assessment included demography, assessment of proteinuria and urinary protein to creatinine ratio, blood pressure measurement and assessment of fasting blood glucose, fasting insulin level, lipid panel and the circulating levels of malondialdehyde, resistin, vaspin, interleukin-18 and asymmetric dimethyl arginine.

Preeclamptic women showed more atherogenic lipid profile, significantly higher Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and significantly elevated levels of malondialdehyde, resistin, vaspin and interleukin-18 than the other study groups. Serum asymmetric dimethyl arginine concentration showed non-significant difference among the three study groups. The levels of resistin and vaspin showed significant decrease four weeks postpartum in preeclamptic group.

We concluded that, preeclampsia was associated with insulin resistance, dyslipidemia, oxidative stress, inflammation and significant changes in adipokines; resistin and vaspin. Furthermore, the significant increase in the serum levels of resistin and vaspin at the third trimester and their significant decline four weeks postpartum in preeclamptic group focus the attention on the role played by these adipokines in the pathogenesis of preeclampsia.

Keywords: Asymmetric dimethyl arginine; Interleukin-18; Malondialdehyde; Preeclampsia; Resistin; Vaspin

Highlights:
- Preeclampsia was associated with insulin resistance; dyslipidemia, lipid peroxidation and inflammation giving suggestion about the role played by insulin resistance, dyslipidemia, lipid peroxidation and inflammation in the pathogenesis of preeclampsia.
- Significant increase in the serum resistin and vaspin levels at third trimester which tended to decline 4 weeks postpartum was observed in preeclamptic women which focus the attention on the role played by these adipokines during preeclampsia.

Introduction

Preeclampsia is a multi-systemic progressive disorder that occurs after 20 weeks of gestation and may last for 4–6 weeks postpartum. International Society for the Study of Hypertension in Pregnancy (ISSHP) defined preeclampsia as hypertension (blood pressure 140/90 mmHg) coexists with one or more of the following new-onset conditions; proteinuria and maternal organ dysfunction including neurological complications, renal impairment, hematological complications and uteroplacental dysfunction (Tranquilli et al., 2014). Preeclampsia has a negative impact on both mother and fetus and may be associated with maternal mortality (Ghulmiyyah and Sibai, 2012).

The pathogenesis of preeclampsia is related to insulin resistance, lipid metabolism disorder and endothelial dysfunction (Abhari et al., 2014). Oxidative stress is considered as a leading cause for placental vasoconstriction and reduction of uteroplacental circulation that in turn stimulate pro-inflammatory cytokines and anti-angiogenic factors release which participate in endothelial dysfunction and placental hypoxia (de Lucca et al., 2016).

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Asymmetric dimethyl arginine (ADMA) is considered as a mediator of endothelial dysfunction and vascular malfunctions. Therefore, ADMA may serve as a potential biomarker of endothelial dysfunction during preeclampsia (Tousoulis et al., 2015). Resistin and vaspin are adipokines secreted by adipose tissue. Resistin impairs glucose uptake by adipocytes, promotes inflammation and insulin resistance (Steppan et al., 2001). Vaspin is an adipokine which enhances insulin sensitivity and plays a role in glucolipid metabolism (Roca-Rodríguez et al., 2012).

The role which resistin and vaspin play in preeclampsia is still obscure. However, resistin induces endothelial cells activation by promoting endothelin-1 (Verma et al., 2003). Furthermore, resistin increases the expressions of various proinflammatory factors and inhibits endothelial nitric oxide synthase via oxidative stress in human endothelial cells (Chen et al., 2010; Hsu et al., 2011). Proinflammatory cytokines and oxidative stress are involved in the development of the endothelial dysfunction which results in abnormal placentation (Roberts, 1998; Shah and Khalil, 2015). Abnormal placentation, the starting point for the development of preeclampsia leads to placental ischemia and hypoxia with subsequent raised secretion of antiangiogenic factors including soluble fms-like tyrosine kinase-1 (sFlt-1) which antagonize the proangiogenic factors like placental growth factor (PlGF) (Lockwood et al., 2008). This may impair the antiangiogenic proangiogenic balance with subsequent increase in sFlt-1/ PlGF ratio which represents a reliable tool for early prediction and monitoring of preeclampsia (Ohkuchi et al., 2010). On the other hand, vaspin was reported to play an important role in prevention of endothelial injuries, suppression of inflammation and inhibition of reactive oxygen species (Hida et al., 2005; Phalitakul et al., 2011). Therefore, vaspin may provide a protective effect during preeclampsia.

In this context, the present study aimed at examining the metabolic and biochemical changes involved in the pathogenesis of preeclampsia including insulin resistance, lipid metabolism disorder, oxidative stress, adipokines (vaspin and resistin), inflammatory cytokine IL-18 and asymmetric dimethyl arginine (ADMA); a potential biomarker for endothelial dysfunction.

Materials and methods

Study design

This prospective observational cohort study was conducted on a total number of 60 women who were matched for age and BMI and ethnicity. All enrolled women were Egyptians which refers to the ethnic group and the nationality. The women were classified into: 20 apparently healthy non-pregnant women (group 1 or control group; $n = 20$), 20 normally pregnant women (group 2; $n = 20$) and 20 pregnant women with preeclampsia (group 3; $n = 20$) at their third trimester. Preeclampsia was defined and diagnosed by the elevation of blood pressure with systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg in two separate occasions after 20 weeks of gestation in women with previously normal blood pressure. Preeclampsia was also defined by urinary protein to creatinine ratio greater than 0.3 mg/mg. All participants were selected from the Outpatient Clinic of Obstetrics and Gynecology Department at the Menofya University Hospital including the healthy non-pregnant women who were in attendance for their routine medical check-up. The study was performed in accordance with the ethical standards as laid down in the 1964 declaration of Helsinki and its later amendments. The institutional Research Ethics Committee approved the current study (CP0002). The study was registered as a clinical trial with ID: NCT04455204. Written informed consents were taken from all participants. The gestational age was determined conventionally and re-affirmed by ultrasonographic measurement. At enrollment, all participants were assessed and submitted to blood and urine samples collection. The pregnant women were further re-evaluated four weeks after delivery. Exclusion criteria were women with risk factors for oxidative stress such as smokers and those with medical history of diabetes mellitus and tuberculosis. Women with medical history of hypertension, familial hyperlipidemia, liver dysfunction, inflammatory diseases and renal disorder were excluded. Non-pregnant women on hormonal therapy or hormonal contraceptives were also excluded.

Methods

Demographic and anthropometric measurements

A detailed history including age and pregnancy history (parity, gravidity) was taken and the gestational age was determined. Height and weight were measured and body mass index (BMI) was calculated as follow: BMI = [Weight (kg) ÷ Height^2 (m)].

Laboratory analysis

Routine measurements

At enrollment, urine analysis was done on 10–20 ml of freshly voided mid-stream early morning urine samples and proteinuria was immediately assessed using urine dipstick test. Spot mid-stream urine specimens were also used for the determination of Protein: Creatinine Ratio (P/C ratio). Total urine protein concentration was evaluated through pyrogallol-red molybdate colorimetric method (Spectrum Diagnostic, Egypt) and the urinary creatinine concentration was measured by Jaffe colorimetric kinetic method (Spectrum Diagnostic, Egypt). The spot urine P/C ratio was calculated by dividing the urinary protein concentration by the urinary creatinine concentration. Proteinuria was defined as +1 protein value with urine dipstick or a spot urine P/C ratio cut off point of (0.3 mg/mg) (Brown et al., 2001). For each participant, measurement of blood pressure was done in two separate occasions using sphygmomanometer.

Biochemical measurements

At early morning, venous blood was collected from all participants after an overnight fasting. Blood was allowed to clot, centrifuged at 4500 × g for 10 min (Hettich Zentrifugen EBA 20). The serum was divided into two portions; the first portion (fresh sera) was used for immediate determination of fasting blood glucose and lipid profile and the second portion was frozen at −80 °C until biochemical analysis of the remaining parameters. Both total cholesterol (TC) and triglyceride (TG) levels were assayed by enzymatic colorimetric method. High density lipoprotein (HDL-C) was assayed by precipitation method. Low-density lipoprotein cholesterol (LDL-C) and very low density lipoprotein (VLDL) were calculated using the Friedewald formula: [LDL-C = TC − HDL-C − (TG ÷ 5)] and [VLDL = (TG ÷ 5)] provided that TG level is less than 400 mg/dl (Friedewald et al., 1972). Castelli risk index-I (TC/HDL-C) and Castelli risk index-II (LDL/HDL-C) were also calculated. Fasting blood glucose was assayed by glucose oxidase method (Spinreact, Spain). Fasting insulin level was assayed by ELISA kit (DRG International, Inc.). Estimation of insulin resistance (IR) was done using the HOMA-IR index which is defined as fasting insulin (μIU/ml) times fasting glucose (mmol/l) divided by 22.5 or divided by 405 if fasting blood glucose was

expressed in mass units (mg/dl) (Matthews et al., 1985). Malondialdehyde (MDA) level was measured spectrophotometrically using Draper and Hadly method (Draper and Hadley 1990). Serum resistin, vaspin, IL-18 and ADMA concentrations were assayed using commercially available ELISA kits (BioVendor, Immunodignostic AG, eBioscience, Elbascience) according to the manufacturer's instructions.

Statistical analysis

The collected data were statistically analyzed using SPSS software (Statistical Package for the Social Sciences, version 19, SPSS Inc. Chicago, USA). Quantitative data were described as range, mean, standard deviation and median. Qualitative data were described as number and percent and comparison between groups was done using Chi-square test (χ^2). For comparison between means of two groups of parametric data of independent samples, student *t*-test was used. For comparison between means of two groups of non-parametric data of independent samples, Z value of Mann–Whitney test was used. For comparison between means of two related groups (before and after data) of parametric data, paired *t*-test was used. For comparison between more than two means of parametric data, F value of ANOVA test was calculated and scheffe test was used to compare between each two means if F value was significant. Significant level was set at $p < 0.05$.

Results

Tables 1 and 2 illustrate the basic and reproductive data of the study participants. At enrollment, ages and BMI of the women in the three study groups were statistically similar ($p > 0.05$). Non-significant difference in both systolic and diastolic blood pressure was observed between non-pregnant women and women with normal pregnancy ($p > 0.05$). However, both systolic and diastolic blood pressure were significantly elevated in preeclamptic women as compared to the other two groups ($p < 0.0001$). At enrollment, the results obtained from the dipstick test showed absence of proteinuria in both non-pregnant and normally pregnant women. On the other hand, four preeclamptic women (20%) had +1, ten women (50%) had +2, four women (20%) had +3 and two women (10%) had +4. Non-significant difference was observed in urinary P/C ratio between non-pregnant and normally pregnant women ($p = 0.985$). Women with preeclampsia showed significantly higher P/C ratio as compared to non-pregnant and normally pregnant women ($p = 0.000$). At enrollment, there was non-significant difference between the normally pregnant women and those with preeclampsia regarding gestational age ($p = 0.69$), mean gravidity ($p = 0.056$) and mean parity ($p = 0.95$). The gestational age at delivery time was significantly lower in women with preeclampsia as compared to normally pregnant women ($p = 0.0001$). The neonates of the women with preeclampsia showed significantly lower birth weight than the women with normal pregnancy ($p = 0.0001$). Regarding mode of delivery, the number and percent of women who underwent cesarean section were significantly higher in women with preeclampsia as compared to those with normal pregnancy ($p = 0.011$). The time gap between enrollment and delivery time was 3.57 ± 1.45 weeks for normally pregnant women versus 2.35 ± 0.87 weeks for preeclamptic women ($p = 0.009$).

Tables 3 and 4 with Fig. 1 and 2 summarize the biochemical data of the study groups at enrollment. Fasting blood glucose, fasting insulin level and HOMA-IR index were significantly elevated in preeclamptic group than normally pregnant and non-pregnant groups (P_2&$P_3 = 0.0001$). TC, TG, LDL-C and VLDL were significantly elevated in preeclamptic women than the other two groups. Also, normally pregnant women showed significantly higher levels of TC, TG, VLDL and HDL-C than non-pregnant group. Mean HDL-C level was significantly higher in normally pregnant women than preeclamptic women ($P_3 = 0.0001$). Castelli risk indices I and II were significantly higher in preeclamptic women than normally pregnant and non-pregnant women (P_2&$P_3 = 0.0001$).

Table 1. Basic data of the three study groups ($n = 60$)

Parameter	Non-pregnant women (G1; $n = 20$)	Normally pregnant women (G2; $n = 20$)	Pregnant women with preeclampsia (G3; $n = 20$)	F value	*P*
Age (years)					
Range	23.00–38.00	19.00–38.00	20.00–45.00	3.123	0.052
Mean ± SD	29.75 ± 4.69	26.25 ± 5.27	30.50 ± 7.01		
Median	29.00	25.00	30.00		
BMI (kg/m^2)					
Range	22.70–35.20	25.80–35.50	25.30–41.60	2.901	0.063
Mean ± SD	28.66 ± 3.21	30.18 ± 2.54	31.37 ± 4.61		
Median	27.10	29.70	30.25		
SBP (mmHg)					
Range	100–120	90–120	140–190	98.7	<0.0001*
Mean ± SD	114.50 ± 6.86	112.00 ± 8.94	156.50 ± 15.90		
Median	120	110	150		
DBP (mmHg)					
Range	70–85	60–80	90–110	89.15	<0.0001*
Mean ± SD	76.25 ± 5.10	74.75 ± 6.78	98.75 ± 7.05		
Median	80	80	100		
U. P/C ratio (mg/mg)					
Range	0.12–0.47	0.13–0.49	0.36–1.10	59.836	0.000*
Mean ± SD	0.222 ± 0.083	0.23 ± 0.089	0.68 ± 0.233		

Data are presented as range, mean ± SD and median. BMI: body mass index; SBP: Systolic blood pressure; DBP: diastolic blood Pressure; U. P/C ratio: Urinary protein to creatinine ratio. Significance level was set at $p < 0.05$. * Significant difference.

Table 2. Reproductive data of the study participants

Parameter	Non-pregnant women (G1; *n* = 20)	Normally pregnant women (G2; *n* = 20)	Pregnant women with preeclampsia (G3; *n* = 20)	Z value	*P*
Gravidity					
Range	–	2–6	3–6	0.349	0.056
Mean ± SD		3.00 ± 1.32	3.00 ± 1.43		
Parity					
Range	–	0-4	0-4	0.056	0.955
Mean ± SD		2.00 ± 1.32	2.00 ± 1.13		
				t-test	*P*
Gestational age at enrollment (weeks)					
Range	–	32.00–38.00	31.00–36.00	0.16	0.69
Mean ± SD		35.84 ± 1.59	34.45 ± 1.54		
Median		36.00	35.00		
Gestational age at delivery (weeks)					
Range	–	38.00–41.00	34.00–38.00	3.849	0.0001*
Mean ± SD		39.40 ± 0.99	36.80 ± 1.32		
Median		39.00	37.00		
Birth weight (kg)					
Range	–	2.74–3.45	1.92–2.95	3.883	0.0001*
Mean ± SD		3.08 ± 0.21	2.49 ± 0.28		
Median		3.11	2.50		

Mode of delivery	Number	Percent	Number	Percent	χ^2 value	*P*
CS	5	25	14	70		
ND	15	75	6	30	6.420	0.011*

Data are presented as range, mean ± SD, median, number and percent. Cs: cesarean section; ND: normal delivery; Z value: Z value of Mann–Whitney test, χ^2: Chi Square test. * Significant difference ($p < 0.05$).

Table 3. Glycemic and lipid panels among the three study groups at enrollment (*n* = 60)

Laboratory findings	Non-pregnant women (G1; *n* = 20)	Normally pregnant women (G2; *n* = 20)	Pregnant women with preeclampsia (G3; *n* = 20)	F value *P*	Scheffe test (*P*)
FPG (mg/dl)	51.00–96.00 69.89 ± 11.07	70.00–105.00 88.50 ± 11.51	74.00–144.00 112.80 ± 15.94	54.553 0.000*	P_1&P_2 = 0.0001* P_3 = 0.0001*
FPI (μIU/ml)	1.10–8.40 4.60 ± 1.95	5.60–17.10 10.22 ± 3.75	8.40–34.10 20.18 ± 6.89	57.115 0.0001*	P_1 = 0.002* P_2&P_3 = 0.0001*
HOMA-IR index	0.19–1.52 0.79 ± 0.37	1.09–3.89 2.24 ± 0.88	2.18–11.37 5.72 ± 2.18	67.876 0.0001*	P_1 = 0.006* P_2&P_3 = 0.0001*
TC (mg/ml)	99.00–210.00 159.55 ± 35.40	173.00–250.00 208.00 ± 24.75	209.00–290.00 245.90 ± 23.91	46.109 0.0001*	P_1&P_2 = 0.0001* P_3 = 0.0001*
TG (mg/dl)	54.00–195.00 117.45 ± 42.44	126.00–230.00 176.7 ± 27.99	143.00–295.00 219.8±39.18	38.416 0.0001*	P_1 = 0.002* P_2 = 0.0001* P_3 = 0.002*
HDL-C (mg/dl)	22.00–77.00 48.05 ± 14.52	30.00–88.00 63.15 ± 15.42	22.00–74.00 42.50 ± 12.46	11.344 0.0001*	P_1 = 0.006* P_2 = 0.470 P_3=0.0001*
LDL-C (mg/dl)	28.40–155.00 88.01 ± 37.04	50.40–178.00 109.52 ± 33.63	94.50–206.00 156.6 ± 32.11	20.913 0.0001*	P_1 = 0.150 P_2&P_3 = 0.0001*
VLDL (mg/dl)	10.80–39.00 23.49 ± 8.49	25.20–46.00 35.33 ± 5.60	28.60–94.50 47.63 ± 13.18	31.544 0.0001*	P_1&P_3 = 0.001* P_2 = 0.0001*

Data are presented as range, mean ± standard deviation. FPG: Fasting plasma glucose; FPI: Fasting plasma insulin; HOMA-IR: homeostasis model assessment for insulin resistance; TC: total cholesterol; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; VLDL: very low density lipoprotein; LDL-C: low density lipoprotein cholesterol. G1: non-pregnant group; G2: normal pregnant group; G3: preeclamptic group. P_1 indicates significance difference between non-pregnant and normal pregnant group (G1 vs G2); P_2 indicates significance difference between non-pregnant and preeclamptic group (G1 vs G3); P_3 indicates significance difference between normal pregnant and preeclamptic group (G2 vs G3). * Significant difference ($p < 0.05$).

Table 4. Castelli indices, oxidative stress marker, adipokines, inflammatory and endothelial dysfunction markers among the three study groups at enrollment (n = 60)

Laboratory findings	Non-pregnant women (G1; n = 20)	Normally pregnant women (G2; n = 20)	Pregnant women with preeclampsia (G3; n = 20)	F value P	Scheffe test (P)
Castelli index-I (TC/HDL-C)	1.72–7.14 3.67 ± 1.56	1.96–6.57 3.56 ± 1.25	3.34–10.73 6.23 ± 1.86	18.354 0.0001*	P_1 = 0.976 P_2&P_3 = 0.0001*
Castelli index-II (LDL/HDL-C)	0.41–5.65 2.15 ± 1.46	0.57–4.68 1.95 ± 1.06	1.49–7.81 4.04 ± 1.62	13.655 0.0001*	P_1 = 0.904 P_2&P_3 = 0.0001*
MDA (μmole/ml)	1.67–4.62 2.97 ± 0.93	1.89–5.87 3.62 ± 1.07	2.26–6.75 4.65 ± 1.41	10.712 0.0001*	P_1 = 0.217 P_2 = 0.0001* P_3 = 0.024*
Resistin (ng/ml)	3.88–7.75 5.78 ± 1.04	3.55–11.95 6.48 ± 2.00	4.77–15.66 8.80 ± 2.47	13.503 0.0001*	P_1 = 0.520 P_2 = 0.0001* P_3 = 0.002*
Vaspin (ng/ml)	9.05–17.77 13.69 ± 2.43	10.08–18.55 14.57 ± 2.16	9.88–22.53 17.18 ± 3.38	8.946 0.0001*	P_1 = 0.588 P_2 = 0.001* P_3 = 0.014*
IL-18 (pg/ml)	68.32–122.46 92.36 ± 13.53	83.10–127.54 102.62 ± 12.0	83.10–136.22 113.16 ± 15.1	11.676 0.0001*	P_1 = 0.067 P_2&P_3 = 0.0001*
ADMA (μmole/l)	0.24–1.72 0.55 ± 0.34	0.26–1.06 0.59 ± 0.50	0.12–1.03 0.66 ± 0.28	0.610 0.547	P_1 = 0.919 P_2 = 0.553 P_3 = 0.793

Data are presented as range, mean ± standard deviation. ADMA: asymmetric dimethyl arginine; MDA: malondialdehyde, IL-18: interleukin-18. G1: non-pregnant group; G2: normal pregnant group; G3: preeclamptic group. P_1 indicates significance difference between non-pregnant and normal pregnant group (G1 vs G2); P_2 indicates significance difference between non-pregnant and preeclamptic group (G1 vs G3); P_3 indicates significance difference between normal pregnant and preeclamptic group (G2 vs G3). * Significant difference (p < 0.05).

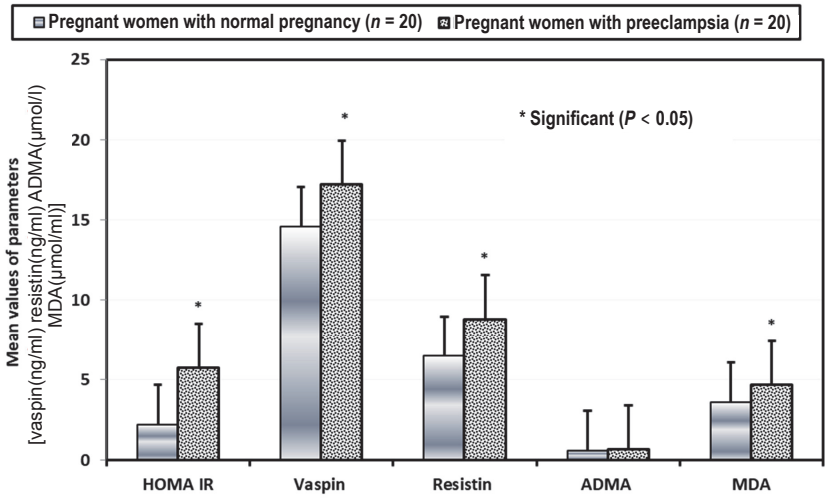

Fig. 1. Mean values of HOMA-IR, vaspin, resistin, ADMA and MDA among the pregnant women with and without preeclampsia during their third trimester of pregnancy

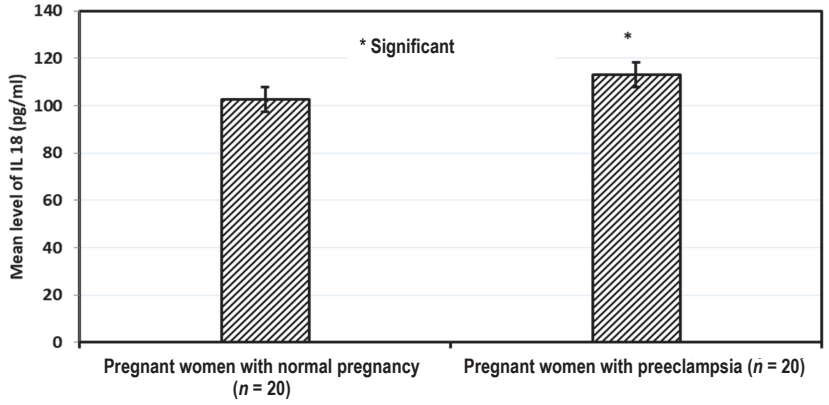

Fig. 2. Mean values of IL-18 among the pregnant women with and without preeclampsia during their third trimester of pregnancy

Serum resistin and vaspin levels were significantly elevated in preeclamptic women than non-pregnant and normally pregnant women ($P < 0.05$). However, the levels of these adipokines were non-significantly elevated in normally pregnant women as compared to non-pregnant women ($P_1 = 0.52$, $P_1 = 0.58$ respectively). Serum MDA and serum IL-18 concentrations were significantly elevated during preeclampsia as compared to the other two groups ($P < 0.05$). The levels of the oxidative stress and inflammatory markers were non-significantly elevated in normally pregnant women as compared to the control group ($P > 0.05$). Serum ADMA concentration showed non-significant difference among all study groups ($P_1 = 0.919$; $P_2 = 0.55$; $P_3 = 0.79$ respectively).

Tables 5 and 6 illustrate the laboratory findings in pregnant women with and without preeclampsia during the third trimester of pregnancy and four weeks after delivery. Four weeks after delivery, the preeclamptic women showed significantly lower fasting blood glucose, insulin level and HOMA-IR index as compared to their third trimester values ($P = 0.004$, $P = 0.0001$, $P = 0.0001$ respectively). As regarding women with normal pregnancy, however blood glucose was non-significantly decreased postpartum ($P = 0.897$), insulin level and HOMA-IR were significantly decreased four weeks after delivery as compared to their third trimester values ($P = 0.001$). In preeclamptic group, TC, TG, LDL-C levels showed non-significant decrease four weeks after delivery as compared to their antepartum levels ($p > 0.05$). In contrast, TC and TG levels showed significant decrease in normally pregnant women after delivery ($P = 0.0001$). Also, VLDL concentration was significantly decreased in pregnant women with or without preeclampsia four weeks after delivery ($p < 0.05$). One month after delivery, Castelli risk indices I and II showed non-significant decrease in preeclamptic group as compared to their third trimester values ($P > 0.05$). As compared to the third trimester data, the preeclamptic women showed non-significant increase in HDL-C concentrations ($P = 0.688$) while normally pregnant women showed significant decrease in HDL-C level ($P = 0.0001$) four weeks after delivery. Serum MDA, IL-18 and ADMA levels were non-significantly changed postpartum in both preeclamptic and normally pregnant women ($P > 0.05$). Although, serum resistin and vaspin levels were significantly decreased four weeks postpartum in preeclamptic group as compared to their third trimester values ($P < 0.05$), women with normal pregnancy showed non-significant decrease in the levels of these adipokines after delivery ($P > 0.05$). Mean values of serum resistin, vaspin, ADMA and MDA among the pregnant women with and without preeclampsia are shown in Fig. 3.

Table 5. Glycemic and lipid panels among pregnant women with and without preeclampsia during their third trimester and four weeks after delivery ($n = 40$)

Laboratory findings	Normally pregnant women (G2; $n = 20$)		Preeclamptic women (G3; $n = 20$)		*t*-test	*P*
	Mean ± SD	Paired *t*-test *P*-value	Mean ± SD	Paired *t*-test *P*-value		
FPG (mg/dl)						
At 3rd trimester	88.50 ± 11.51	0.130	112.8 ± 15.94	3.052	5.527	0.0001*
4 Weeks postpartum	89.00 ± 12.82	0.897	84.00–118.00	0.004*	3.039	0.004*
FPI (μIU/ml)						
At 3rd trimester	10.22 ± 3.75	3.735	20.18 ± 6.89	5.468	5.676	0.0001*
4 Weeks postpartum	6.44 ± 2.53	0.001*	10.90 ± 3.17	0.0001*	4.924	0.0001*
HOMA-IR index						
At 3rd trimester	2.24 ± 0.88	3.448	5.72 ± 2.18	5.858	6.615	0.0001*
4 Weeks postpartum	1.42 ± 0.60	0.001*	2.68 ± 0.79	0.0001*	5.714	0.0001*
TC (mg/dl)						
At 3rd trimester	208.0 ± 24.75	4.536	245.9 ± 23.91	1.288	4.925	0.0001*
4 Weeks postpartum	175.9 ± 19.72	0.0001*	235.95 ± 24.9	0.205	8.448	0.0001*
TG (mg/dl)						
At 3rd trimester	176.7 ± 27.99	6.506	219.8 ± 39.18	1.848	4.003	0.0001*
4 Weeks postpartum	122.2 ± 24.85	0.0001*	200.3 ± 26.07	0.072	9.699	0.0001*
HDL-C (mg/dl)						
At 3rd trimester	63.15 ± 15.42	4. 680	42.50 ± 12.46	0.405	4.658	0.0001*
4 Weeks postpartum	43.30 ± 11.04	0.0001*	44.00 ± 10.92	0.688	0.202	0.841
LDL-C (mg/dl)						
At 3rd trimester	109.5 ± 33.63	0.152	156.6 ± 32.11	0.442	4.531	0.0001*
4 Weeks postpartum	108.2 ± 21.73	0.880	152.4 ± 28.59	0.661	5.508	0.0001*
VLDL (mg/dl)						
At 3rd trimester	35.33 ± 5.60	6.506	47.63 ± 13.18	2.555	3.842	0.0001*
4 Weeks postpartum	24.44 ± 4.97	0.0001*	39.56 ± 5.09	0.015*	9.504	0.0001*

Data are presented as mean ± standard deviation. FPG: Fasting plasma glucose; FPI: Fasting plasma insulin; HOMA-IR: homeostasis model assessment for insulin resistance; TC: total cholesterol; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; VLDL: very low density lipoprotein; LDL-C: low density lipoprotein cholesterol. * Significant difference ($p < 0.05$).

Table 6. Castelli indices, oxidative stress marker, adipokines, inflammatory and endothelial dysfunction markers among pregnant women with and without preeclampsia during their third trimester and four weeks after delivery (n = 40)

Laboratory findings	Normally pregnant women (G2; n = 20)		Preeclamptic women (G3; n = 20)		t-test	P
	Mean ± SD	Paired t-test P-value	Mean ± SD	Paired t-test P-value		
Castelli index-I (TC/HDL-C)						
At 3rd trimester	3.56 ± 1.25	1.827	6.23 ± 1.86	1.035	5.328	0.0001*
4 Weeks postpartum	4.31 ± 1.36	0.076	5.67 ± 1.56	0.307	2.925	0.006*
Castelli index-II (LDL/HDL-C)						
At 3rd trimester	1.95 ± 1.06	2.111	4.04 ± 1.62	0.689	4.842	0.0001*
4 Weeks postpartum	2.72 ± 1.24	0.042*	3.72 ± 1.36	0.495	2.430	0.020*
MDA (µmole/ml)						
At 3rd trimester	3.62 ± 1.07	1.647	4.65 ± 1.41	1.573	2.596	0.013*
4 Weeks postpartum	3.10 ± 0.92	0.108	4.06 ± 0.91	0.124	3.304	0.002*
Resistin (ng/ml)						
At 3rd trimester	6.48 ± 2.00	1.730	8.80 ± 2.47	2.728	3.276	0.002*
4 Weeks postpartum	5.60 ± 1.07	0.092	7.06 ± 1.43	0.010*	3.667	0.001*
Vaspin (ng/ml)						
At 3rd trimester	14.57 ± 2.16	1.908	17.18 ± 3.38	3.156	2.898	0.006*
4 Weeks postpartum	13.33 ± 1.96	0.064	14.44 ± 1.88	0.003*	1.835	0.074
IL-18 (pg/ml)						
At 3rd trimester	102.62 ± 12.0	0.663	113.16 ± 15.1	0.777	2.441	0.019*
4 Weeks postpartum	100.57 ± 6.81	0.511	110.14 ± 8.61	0.442	3.900	0.0001*
ADMA (µmole/l)						
At 3rd trimester	0.59 ± 0.50	0.293	0.66 ± 0.28	0.133	0.736	0.466
4 Weeks postpartum	0.57 ± 0.34	0.771	0.67 ± 0.33	0.895	0.992	0.327

Data are presented as mean ± standard deviation. ADMA: asymmetric dimethyl arginine; MDA: malondialdehyde; IL-18: interleukin-18. * Significant difference ($p < 0.05$).

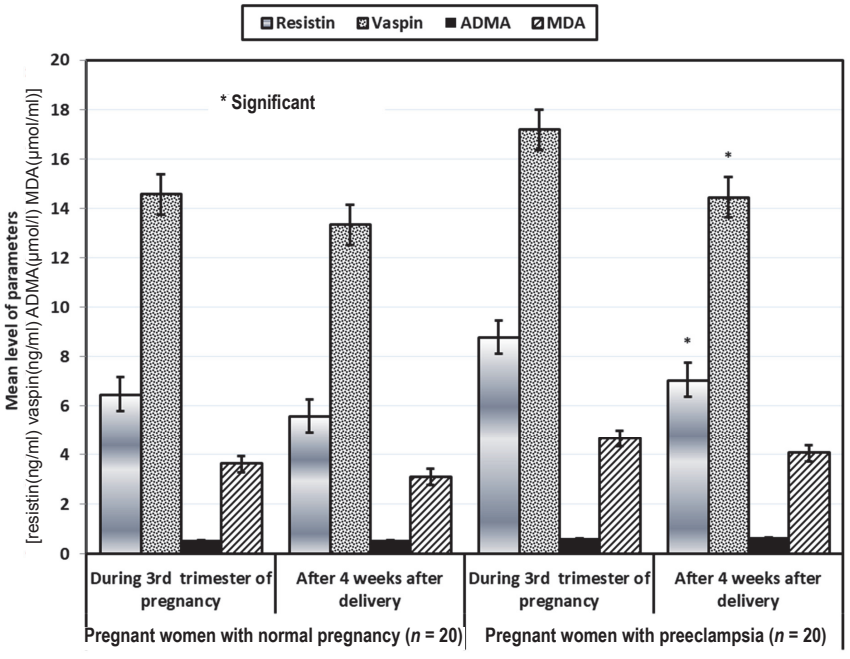

Fig. 3. Mean values of resistin, vaspin, ADMA and MDA among the pregnant women with and without preeclampsia during their third trimester of pregnancy and 4 weeks after delivery

Discussion

Preeclampsia is a pregnancy related complication that can impair both mothers and babies health. Our study illustrates that, all the pregnant women with preeclampsia showed SBP ≥ 140 mmHg and DBP ≥ 90 mmHg, a result seems parallel to previously reported findings (Peres et al., 2018).

Spot urine protein : creatinine ratio was used as an alternative to 24-hour urine protein measurement for the quantitative detection of proteinuria since spot urine protein : creatinine ratio was reported to be goodly correlated with 24 hours proteinuria (Demirci et al., 2015). During the current study, all women with preeclampsia exhibited protienuria on urine dipstick test and showed significantly higher urinary P/C ratio as compared to non-pregnant and normally pregnant women, a result seems in accordance with previously reported findings (Demirci et al., 2015).

Our study revealed that, ante-partum fasting blood glucose level, insulin level and HOMA-IR (the favorable index for insulin resistance) were significantly elevated in preeclamptic women as compared to non-pregnant and normally pregnant women; a result comes in matching with previously reported findings (Girouard et al., 2007). Four weeks after delivery, HOMA-IR index showed significant decrease in pregnant women with or without preeclampsia. The improvement of insulin resistance after delivery is attributed to the removal of the placenta which releases certain hormones that may counteract insulin action (Ryan and Enns, 1988). In this context, insulin resistance may be involved in the pathogenesis of preeclampsia and may represent one of the risk factors that can help in the prediction of preeclampsia.

During the third trimester of pregnancy, HDL-C level was significantly lower while TC, TG, LDL-C and VLDL levels were significantly higher in preeclamptic group than non-pregnant and normally pregnant groups. Our finding concerning HDL-C is in matching with formerly reported findings (Islam et al., 2010). The observed elevation of LDL-C level in preeclamptic women may be attributed to elevated estrogen and progesterone levels during preeclampsia (Salameh and Mastrogiannis, 1994). The observed higher VLDL level in preeclamptic women may be attributed to hypertriglyceridemia since VLDL is well known to transport TG in peripheral blood. Our result concerning VLDL comes in consonance with formerly reported findings (Herrera et al., 1988). The observed atherogenic lipid profile in preeclamptic women during the current study confirms the notion that, the impairment of the lipoprotein metabolism may play a critical role in the pathogenesis of preeclampsia and in the development of insulin resistance (Bassi et al., 2011). Hypertriglyceridemia with subsequent triglycerides accumulation can result in lipotoxicity and oxidative stress with subsequent impairment of glucose-stimulated insulin secretion and insulin resistance (Bassi et al., 2011). Castelli risk index I (CRI-I = TC/HDL) and Castelli risk index II (CRI-II = LDL/HDL) are more accurate risk predictors of coronary artery disease (CAD) than individual lipid parameters (Kannel, 2005). During the current study, preeclamptic women showed significantly higher CRI-I and CRI-II than normally pregnant and non-pregnant women suggesting their susceptibility for CAD and cardiovascular complications. Our result seems in accordance with previously reported findings revealed that; TC/HDL ratio was significantly increased in women with preeclampsia as compared to normally pregnant women (Singh et al., 2015).

Preeclampsia is associated with increased oxidative stress and reduced placental antioxidant enzyme activity with subsequent endothelial dysfunction and oxidative injury in both maternal and placental compartment (Bassi et al., 2011). The present data revealed that, MDA level was significantly higher in preeclamptic women than non-pregnant and normally pregnant women. Our result is in parallel with a former study postulated that, MDA level was elevated during preeclampsia as compared to normal pregnancy secondary to abnormally increased lipid peroxides formation by placenta during preeclampsia (Fenzl et al., 2013). During the current study, serum MDA concentrations tended to be decreased in both pregnancy groups after delivery. Our findings are in matching with aforementioned data postulated that, pregnancy is a stressful condition associated with accumulation of oxidative stress markers which may play a considerable role in the development of insulin resistance (Bassi et al., 2011).

Resistin is an adipokine secreted by macrophages, monocytes and white adipose tissue. Resistin promotes inflammation and contributes to insulin resistance through AMP-activated protein kinase dependent and independent mechanisms (Roca-Rodríguez et al., 2012; Yura et al., 2003). Our data postulated that, circulating resistin level was significantly higher in preeclamptic group than the other two groups and its level showed significant decline four weeks after delivery. Our former result comes in accordance with previously reported findings (Seol et al., 2010). These aforementioned data suggest that, the elevation of resistin level during preeclampsia is not only related to increased secretions from placenta and adipose tissue but also may be attributed to other sources responsible for increased circulating resistin level. Monocytes which are regulated by many inflammatory cytokines may represent another source for circulating resistin (Kaser et al., 2003). Preeclampsia is a systemic inflammatory disease associated with monocytes activation, therefore the observed elevation in resistin level during preeclampsia may be attributed to the systemic inflammatory response (Filková et al., 2009). Vaspin is an adipokine which sensitizes insulin and regulates endogenous glucose metabolism (Hida et al., 2005). We observed that, circulating vaspin was significantly elevated in preeclamptic women than normally pregnant and non-pregnant women and its level showed significant decline four weeks after delivery in women with preeclampsia. The significant elevation of serum vaspin concentration in preeclamptic women during their third trimester may be attributed to a compensatory protective mechanism against insulin resistance and inflammation through the anti-inflammatory activity of vaspin (Hida et al., 2005). In contradiction with our finding, Stepan et al. (2010) reported that, there was non-significant difference in circulating vaspin levels between preeclamptic women and women in the control group (Stepan et al., 2010).

Interleukin-18 originally described as interferon gamma (IFN-c) inducing factor is a pro-inflammatory cytokine which may be associated with both inflammation and insulin resistance. IFN-c could inhibit the migration and invasion of cytotrophoblasts and triggers spiral artery modification which may be related to the etiology of the preeclampsia (Monk et al., 2005). Serum IL-18 concentration was significantly elevated during preeclampsia than non-pregnant and normally pregnant women. This elevation of IL-18 in women with preeclamsia may be attributed to preeclampsia associated systemic inflammatory response. The result obtained with IL-18 during the current study is in matching with other authors who reported higher IL-18 level during preeclampsia as compared to

normal pregnancy (Seol et al., 2009). In contrast, our result seems in disagreement with a previously reported finding reported lower IL-18 level in preeclamptic women as compared to normotensive pregnant controls (Laskowska et al., 2011).

The endogenous inhibitor of nitric oxide synthesis, asymmetric dimethyl arginine (ADMA) may represent an important factor for endothelial dysfunction during pregnancy (Slaghekke et al., 2006). ADMA concentrations showed non-significant difference among all study groups. In addition, there was non-significant difference between post-partum and third trimester ADMA concentrations for both pregnant groups. Our former result may be attributed to a state of possible vasodilation that may occur during pregnancy. Our finding comes in matching with a previously reported finding reported absence of significant difference in circulating ADMA concentration among women with preeclampsia, normally pregnant women and non-pregnant women (Silver et al., 1996). However, our result seems in contradiction with other former finding demonstrated abnormal decline in ADMA concentration during pregnancy (Begum et al., 1996).

During the current study, preeclamptic women showed earlier delivery with low birth weight neonates and the majority of them underwent cesarean section for delivery. These consequences may be attributed to preeclampsia associated insulin resistance, dyslipidemia, oxidative stress and inflammation. Therefore, practitioners should consider regular women's prenatal clinic visits for monitoring of their blood pressures, asking for regular screening of proteinuria, evaluation of blood glucose, assessment of sFlt-1/ PlGF ratio and evaluation of lipid panel with management of hyperlipidemia. Although, there are discrepancies about their teratogenicity (Edison and Muenke, 2004; Winterfeld et al., 2013), statin derivatives are still used during preeclampsia for their antihyperlipidemic effect and their lipid independent pleiotropic effects. Statin derivatives diminish inflammation and oxidative stress, inhibit the coagulation cascade and protect the endothelium (Girardi, 2014). Statins may increase the expression of Heme Oxygenase-1 (Hmox-1), the enzyme with anti-inflammatory and antioxidant properties. Stimulated Hmox-1 inhibits the antiangiogenic factors soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) and directly improves endothelial dysfunction (Brownfoot et al., 2015). To minimize the negative outcome, pravastatin the more hydrophilic statin derivative unable to pass through the placenta may represent a suitable candidate to be used for preeclampsia (Ahmed et al., 2020; Winterfeld et al., 2013).

Finally, it is worth mentioning that, the sample size used during the current study was based on some previous studies conducted on preeclampsia (Speer et al., 2008). Furthermore, the points of strength of our study include its cohort prospective design and the assessment of many biological markers which may be involved in the pathogenesis of preeclampsia.

Conclusions

The data obtained during the current study revealed that, preeclampsia was associated with insulin resistance, dyslipidemia, oxidative stress and inflammation suggesting their role in the pathogenesis of preeclampsia. Furthermore, the significant elevation of serum resistin and vaspin levels during the third trimester of pregnancy and their significant decline four weeks after delivery in preeclamptic women focus the attention on the role played by these adipokines in the pathogenesis of preeclampsia. However, large scale studies are still required.

Study limitation

The relatively small sample size represents the main limitation of the current study.

Conflict of interests

The authors declare that, there is no conflict of interests.

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Author contributions

Tarek Mohamed Mostafa, reviewed the literature, constructed the study design. Assessment and enrolment of participants was carried out by Haitham Aboali Hamza. Amany Yasseen Talab collected the clinical data and required samples. Amany Yasseen Talab and Tarek Mohamed Mostafa performed laboratory investigation of collected samples. All authors shared in performing statistical analysis and writing the manuscript. All authors approved the final manuscript.

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