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The Value of Doppler Ultrasound and Serum Lipids in The Prediction of Pregnancy Induced Hypertension

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ABSTRACT

This is a prospective controlled study of the value of the Doppler indices and serum lipids in the anticipation of the occurrence of pregnancy induced hypertension in pregnant female in Ismailia Egypt.

The study was carried out during the period from first of September 1997 till the end of January 2001. The material of this study were 140 cases selected from the out-patient clinic of Suez Canal University Hospital and divided into two groups; the high risk group of 49 cases and the low risk group of 91 cases.

The methods adopted in this study are clinical evaluation and ultrasound examination in a weekly basis starting from the begining of the second trimester to the third trimester inclusive. Estimation of the serum lipids at the first visit and at the third trimester was performed in all cases.

The results of this study showed that 22 cases developed PIH during the study; 13 cases (26.5%) of the hig -risk cases and 9 (9.9%) amoung the low risk group of cases. The difference between the two groups was highly significant in the results of the serum lipids and the Doppler indices studied.

In conclusion, this study proved the significance of the Doppler indices and serum lipids in the prediction of pregnancy induced hypertension among high-risk pregnant population.

INTRODUCTION

Pregnancy induced hypertension (PIH) is one of the most frequently ocurring disorders during pregnancy and its reported incidence is 6-30% world wide [1]. It is a leading cause of maternal mortality and morbidity particularly in underdeveloped countries.[2] In addition it is a major cause of pretem delivery, fetal growth retardation and perinatal mortality.

Intrauterine growth retardation, low birthweight, fetal death and neonatal deaths due to complications of preterm delivery are common perinatal outcomes associated with hypertensive pregnancies. Not only is PIH unpredictable in onset and progression, it is incurable except by termination of pregnancy. Epidemiological risk factors include nulliparity, previous preeclampsia, black race, prepregnancy obesity, diabetes mellitus and multifetal pregnancies.[3,4]

Every aspect of lipid metabolism is influenced by pregnancy. Maternal serum of plasma cholesterol and triglyceride (TG) concentrations increase (1.5 - and threefold, respectively) during pregnancy, with the major increase occurring in the second and third trimesters of pregnancy.[5] Nelson et al showed that the triglyceride content in the placentas delivered in women with preeclampsia is significantly higher that that in controls.[6] Potter and Nestel reported that preeclamptics had on average, much higher levels of circulating triglycerides compared to normotensive pregnant women at delivery.[7]

Normal human pregnancy therefore results in a

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pronounced plasma cholesterol (CH) concentration rises by approximately 25% while TG concentration increases two to three folds. These changes probably reflect deposition of fat during the first half of pregnancy and increases production of CH and low-density lipoproteins (LDL) by the liver for steroid hormone synthesis late in pregnancy.[8]

Hyperlipidaemia can compromise endothelial function and this may contribute to the development of atherosclerotic vascular disease.[9] Human pregnancy is associated with pronounced physiological hyperlipidaemia.[10] In complicated pregnancies the mechanisms regulating physiologic hyperlipidaemia may malfunction. Abnormal lipid profiles and species may have a role in the promotion of oxidative stress and vascular dysfunction seen in preeclampsia. [12]

We are not aware of published reports of maternal lipid and lipoprotein profiles in Epyptian normotensive women and in those presenting with PIH, though investigations have speculated that unhealthy diets and lifestyle characteristics may be important determinants of PIH and preeclampsia.[13] This study was carried out to evaluate changes in lipid profile in Egyptian women during normal pregnancy and the eventual role of these changes in the pathophysiology of PIH.

AIM OF THE STUDY

The aim of this research was to investigate the ability to use the serum lipids profile and Doppler velocimetry for the characterization of the future development of PIH.

MATERIALS AND METHODS

This is a prospective cohort study of the value of using bilateral uterine artery colored Dopper flow velocimetry waveforms (FVWs) and serum lipid profile in prediction of PIH.

The study was conducted in the outpatient clinic of Department of Obstetries and Gynecology and the Radiology Department, Suez Canal University Hospital (SCUH) during the period from the first of September 1997 to the end of January 2001.

The cohort consisted of a statistically significant number of pregnant woment selected from women attending the (ANC) clinic of the SCUH. The study group consists of 2 major groups.

1. Low risk group: 91 pregnant females who enrolled according to the following criteria of eligibility:
- Age: 16-48 years
- Parity: nulliparous women.
- Gestational age >14 weeks confirmed by sure date and diagnostic ultrasound.
- Normotensives: blood pressure <[135/85mmHg]
- No proteinuria <30 mg per 24 hour urine collection
- <+1 by dipstick test

2. High risk group: include 49 pregnant females, of any parity having one of the risk factors for PIH[4]

1- Past history of PIH in previous pregnancies.
2- Past history of diagnosed chronic hypertension.
3- Family history of PIH.
4- History of disturbed lipid profile.
5- Twin pregnancy.
6- Past history of diabetes mellitus or gestational diabetes.

Women enrolled in the study started their 1st visit in the begining of the second trimester they were subjected to the following:

I- Base line clinic visit schedule:
- Complete history taking
- Complete general and obsterical examinations.
- Laboratory investigations including:

1- Complete urine analysis.
2- Fasting and port-prandial blood glucose level.
3- Serum uric acid.
4- Corrected creatining clearances.

Exclusion criteria:
- Women with obstetric and fetal complications (hydrops fetalis or congenital fetal anomalies incompatible with life).
- Cigarette smokers, obese[14] disturbed lipid profile, renal diseases.[15] Proteinuria ≥300mg in 24 hours urine collection.

II- Measuring blood pressure:

This was carried out according to the standards for measuring the blood pressure.[16] The mean arterial blood pressure MAP was recorded in each visit and diagnosis of PIH will be made according to the following:[1]

1) Increase of 30mgHg mean systolic (SBP) or 15mmHg mean diastolic pressure (DBP) compared to value obtained before 20 weeks gestation (first visit).

2) Proteinuria detected by dipsticks defined in the study as present (+ve) or absent (-ve)

III Lipid profile:

Lipids profile was carried out according to the standard test[17] then analysed for:-
- Total cholesterol (reference value 240-400 mg/dl)
- LDL cholesterol (reference value 160-200 mg/dl)
- HDL cholesterol (reference value 80-100 mg/dl)
- Triglycerides (reference value -260mg/dl)

All the study participants were followed weekly for routine ANC.
- Ultrasound examination and serum lipid profile measurements were estimated in the first visit and the beginning of the third trimester.
- The protocol of the study was explained to each participant and enrollment was done according to their will.

Ultrasound examination:

- Using an Accuson 128x-P110 (Accuss on Mountain view) California, USA. the machine was equipped with 3.5MHz convex linear transducer used for all measurements. Using real time and pulsed wave mode facilities to:
  a) Assess fetal growth.
  b) Confirm gestational age by estimating fetal measurements of BPD, FL, HC, AC and EFW.
  c) Determination of the site of the ascending branch of the uterine artery on each side of the cervix.[18]
  d) Calculating uterine artery Doppler Felow velocity wave forms (FVW):
  The three indices calculated were;
  a) The systolic- diastolic ration S/D = A/B (positive if>2.6)
  b) The resistance index RI = A-B/A (positive if>0.65)
  c) The plasticity index PI = A-B/Mean velocity. (Positive if>1.5)

The mean of each was obtained from 3 consecutive calculations of the waveforms.
The difference between the two uterine vessels should not exceed one in any of the measures FVW.[19]
The FVWs considered abnormal according to the following :

i- Persistent abnormal indices.
ii- A persistent notch.
iii-A significant difference between the indices of the two vessels.[20]

All Doppler FVW examinations were performed by a single investigator to exclude the inter-observer error and both abdominal and vaginal probes were used in all cases.
The data from the patients history, examination, lipid profile and Doppler indices were collected and analyzed using the mean, standard deviation, t-test for comparison between the variable, chi-squre Person correlation coefficient and ANOVA test.
Preeclampsia developed in 9.9% of women in group I and 26.5% in group 2. The results of this study are presented in the accompanying tables.

RESULTS AND DISCUSSION

It is well recognized that pregnant women with multiple fetuses, previous preeclampsia, eclampsia, chronic hypertension, insulin dependent diabetes and previous poor pregnancy outcome are at increased risk for PIH.[21]
The medical community also recognizes that nulliparous women constitute the majority of all cases of preeclampsia.[22] In this study, preeclampsia developed in 9.9% of women in group I and 26.5% in group 2.
Other risk factors identified include the extremes of age, race, socioeconomic status, change in paternity blood group and type, previous miscarriage, smoking and alcohol use during pregnancy, increased body mass index, increased systolic and diastolic blood pressure early in pregnancy and increased rate of weight gain during pregnancy.[23]
Disturbed lipid metabolism was noted to be a feature of PIH as early as 1936.[24] Supernormal increases in serum triglycerides and fatty acids develop as early as 10 weeks gestation in women destined to develop PIH.[25] Current evidence suggests that the pathogenesis of preeclampsia involves circulating plasma constituents that can induce endothelial cell activation and/or dysfunction.[26]
The introduction of Doppler ultrasound technology promised non-invasive, safe, repeatable assessment of human and fetal blood fow.[27] Recently Doppler studies proved with a reasonable degree of confidence, the association between PIH and vascular changes at the placental bed, umbilical artery and uterine artery.[28] Abnormal uterine artery FVWs was found to correlate well with abnormal pregnancy outcome in patients with PIH.[29]
However, others found that many women with servere hypertension had normal uteroplacental artery FVWs. PIH was anticipated antenatally through the presence of a significant increase in total serum lipids in early pregnancy and this was further supported by the pressence of abnormal uterine artery waveforms.[25]
In this study we attempted to identify the possibility of using serum lipids profile and Doppler FVWs of the uterine artery to anticipate the possibility of future development of PIH in 140 Egyptian women.
All subjects had baseline ANC, serum lipid profile and uterine artery Doppler FVWs performed in each visit.
The demographic data in Table 1 shows a statistically significant difference between the high risk and low risk groups. The high-risk cases were of higher mean age, higher mean gravidity, parity and abortions. Their mean BMI was also higher indicating that they really fulfilled the inclusion criteria of the study.
Supportive to the results of this study serveral studies[30] have found that PIH is more common in women whose pregnancy occurs at an older maternal age, and those with previous abortion or miscarriage.[31]
Contrary to the results of this study, some investigators observed that PIH is more common in primigravidas and has no relation to abortion or miscarriage.[32] Again the BMI in this study had no relation to the subsequent development of PIH which also contradicts many other studies.[3] This could be due to the different population or the inclusion and exclusion criteria.
While the working status was not a risk factor in this study (table 2), the previous history of PIH or hypertension in the family or the patient herself are frequently reported risk factors in this study and in

Table 1 : Distribution of the cases according to the demographic data.

	Low risk group (n=91)			High risk group (n=49)			P Value
	Mean	±S.D	Range	Mean	±S.D	Range	
Age	24.7	5.8	17-36	29.9	7.6	19-48	<0.05
Gravidity	1.5	.8	1-4	3.6	2.1	1-10	<0.05
Parity	0.2	.5	0-2	2.0	1.6	0-7	<0.05
Abortion	0.4	.5	0-2	0.6	1.1	0-5	>0.05
BMIst visit	32.9	7.0	19.80-53.10	35.6	8.6	21.8-61	<0.05
BMI2nd visit	43.7	9.1	28.40-71.20	46.2	10.2	25.6-80.6	>0.05

P>0.05 Insigificant, P<0.05 significant

Table 2 : Distribution of the low and high risk groups according to occupation.

Occupation	Low risk group		High risk group	
	N	%	N	%
Housewife	60	65.9	33	67.3
Employer	25	27.5	16	32.7
Student	6	6.6	-	-

Table 3 : Distribution of high risk group according to risk factors.

	N	%
Previous history of Preeclampsia	29	59.2
History of essential hypertension	16	30.6
Family history of preeclampsia	7	14.3

Table 4 : The statistical differences between the normal and high-risk groups in blood pressure values (mmHg).

		Low risk group (n=91)			High risk group (n=49)			P Value
		Mean	±S.D	Range	Mean	±S.D	Range	
First vist	SBP	113.0	16.1	70-160	126.2	21.0	80-160	<0.05
	DBP	74.0	11.9	50-90	80.4	13.6	50-100	<0.05
	MAP	87.2	12.9	56.7-120	95.8	15.8	60-120	<0.05
Second vist	SBP	126.5	17.4	90-170	137.0	27.6	100-220	>0.05
	DBP	81.3	11,7	60-120	86.9	19.3	60-140	<0.05
	MAP	96.4	13.3	73.3-136.7	103.7	21.5	73.3-100.7	>0.05

P<0.05 significant

Table 5 : Distribution of the low and high risk groups according to presence of proteinuria or edema.

	Low risk group				High risk group				P Value
	Present		Absent		Present		Absent		
	N	%	N	%	N	%	N	%	
Edema 1st visit	2	2.2	89	97.8	1	2.0	48	98.0	>0.05
Edema 2nd visit	17	18.7	74	81.3	18	36.7	31	63.3	>0.05
Proteinuria 1st visit	1	1.1	90	98.9	1	2.0	48	98.0	>0.05
Proteinuria 2nd visit	17	18.7	74	81.3	16	32.7	33	67.3	<0.05

Table 6 : The statistical analyses between the low risk and high-risk groups as regard lipid profile.

		Low risk group (n=91)			High risk group (n=49)			P Value
		Mean	±S.D	Range	Mean	±S.D	Range	
CH (mg/d1)	1st vist	209.4	61.2	110-420	231-8	57.9	150-380	<0.05
TG (mg/d1)		186.3	71.8	74-580	202.2	70.7	110-490	>0.05
HDL (mg/d1)		44.3	29.9	13-145	47.8	22.1	15-95	>0.05
LDL (mg/d1)		98.9	39.8	34-210	102.8	33.4	60-195	>0.05
CH (mg/d1)	2nd vist	281.4	79.9	160-591	288.4	55.3	177-410	>0.05
TG (mg/d1)		255.5	79.8	111-772	283.1	70.5	200-521	<0.05
HDL (mg/d1)		61.5	33.8	25-190	71.2	28.0	30-173	>0.05
LDL (mg.d1)		133.8	45.7	45-291	145.3	46.1	61-291	>0.05

P>0.05 Insigificant, P<0.05 significant

Table 7 : The statistical difference between the low and high-risk groups as regard Doppler indices

			Low risk group (n=91)			High risk group (n=49)			P Value
			Mean	±S.D	Range	Mean	±S.D	Range	
1st vist	Right side	RI	.6	.8	.44-.86	.6	.1	.4-.9	<0.05
		PI	1.1	.6	.01-4.9	1.3	.7	.2-4.4	>0.05
		S/D	2.4	1.1	1.0-7.1	3.0	1.6	1.1-9.4	<0.05
	Left side	RI	.6	.9	.4-.9	.6	.8	.5-.9	<0.05
		PI	1.1	.4	.6-3.3	1.3	.5	.8-3.2	<0.05
		S/D	2.4	.8	1.3-6.3	3.0	1.3	.2-6.8	<0.05
2nd vist	Right side	RI	.6	.9	.4-.9	.7	.1	.5-.9	<0.05
		PI	1.4	.6	.6-3.3	1.6	.8	.9-5.0	>0.05
		S/D	2.9	1.7	1.1-9.4	3.7	2.1	2.1-10.9	<0.05
	Left side	RI	.6	.9	.4-.9	.7	.9	.6-.9	<0.05
		PI	1.4	.6	.5-4.3	1.7	.9	.8-4.3	<0.05
		S/D	2.8	1.4	1.6-10.5	3.7	2.3	2.2-10.7	<0.05

P>0.05 Insigificant, P<0.05 significant

Table 8 : Distribution of the low and high risk group according to the development of PIH.

	Low risk group		High risk group	
	N	%	N	%
Non -PIH	82	90.1	36	73.5
PIH	9	9.9	11	26.5

X^2=6.7 P<0.05

Table 9 : Characterization of the cases developing PIH (n=22) compared to cases did not develop PIH

	Non-PIH cases (n=118)		Cases who developed PIH (22)		Significance
	Mean	S.D	Mean	S.D	
Age	26.5	6.7	26.7	8.2	>0.05
Gravidity	2.5	1.7	2.2	1.9	>0.05
Parity	0.8	1.4	0.7	1.1	>0.05
Abortion	0.4	0.8	0.5	1.1	>0.05
Weight (Kgm)	83.9	8.5	89.7	11.2	<0.05
BMI	43.6	8.7	49.8	12.2	>0.05
SBP	124.2	16.5	175.9	66.6	<0.05
DBP	78.6	10.0	108.4	12	<0.05
MAP	93.8	11.5	130.9	24.4	<0.05
CH mg/d1	269.0	59.8	363.0	74.9	<0.05
TG mg/d1	245.8	46.3	366.6	120.4	<0.05
HDL mg/d1	55.2	17.5	116.6	42.0	<0.05
LDL mg/d1	128.1	39.1	189.6	47.6	<0.05

Table 10 : Distribution of uterine artery Doppler indices in non-PIH and PIH groups.

				PIH group		Significance
		Mean	±S.D	Mean	±S.D	
Right uterine artery	RI	0.60	0.6	0.9	0.5	<0.05
	PI	1.3	0.3	2.7	0.7	<0.05
	S/D ratio	2.5	0.5	6.8	2.1	<0.05
Left uterine artery	RI	0.6	0.6	0.8	0.9	<0.05
	PI	1.3	0.3	2.6	1.0	<0.05
	S/D	2.5	0.5	6.4	2.6	<0.05

Table 11 : Correlation between lipid profiles and Doppler indices

	Cholesterol	Triglycerides	HDL	LDL	RI right	PI right	S/D right	RI left	PI left	S/D ratio
Cholesterol										
Triglycerides	0.604*									
HDL	0.511*	0.541*								
LDL	0.610*	0.491*	0.549*							
RI right	0.503*	0.532*	0.621*	0.564*						
PI right	0.515*	0.504*	0.649*	0.466*	0.805*					
S/D right	0.480*	0.487*	0.618*	0.418*	0.847*	0.769*				
RI left	0.438*	0.518*	0.496*	0.426*	0.711*	0.661*	0.717*			
PI left	0.468*	0.579*	0.607*	0.480*	0.677*	0.804*	0.659*	0.737*		
S/D left	0.466*	0.606*	0.644*	0.526*	0.707*	0.767*	0.734*	0.744*	0.902*	

* Sibnificant at P<0.05

Table 12 : The percentage of the sensitivity, specificity, accuracy, positive and negative predictive values of all the variables in this study

	Ch%	TG%	HDL%	LDL%	RI%	PI%	S/D%	DI%	DIN%
Sensitivity	30.8	100	59.1	31.8	100	100	100	100	45.5
Specificity	100	75.8	98.3	99.2	94.9	48.7	89.8	76.3	99.2
Accuracy	94	67.4	89.6	93.9	82.7	75.3	79	69.1	90.9
+ve pv	100	50	86.7	87.8	78.6	55	64.7	44	90.7
-ve pv	86.8	100	92.8	88.6	100	100	100	100	92

Cholesterol (CH), triglycerides (TG), high density lipoproteins (HDL), low density lipoproteins (LDL), resistance index (RI), pulstility index (PI), systolic diastolic ratio (S/D), all Doppler indices (DI) and all Doppler indices with diastolic notch (DIN)

TG, RI, PI, S/D and DI are 100% sensitive. CH, HDL, LDL, RI and DIN are > 90% specific. CH, HDL, DIN are > 90% accurate. CH, DIN are > 90% with positive predictive value. While TG, RI, PI, S/D are 100% with negative predictive value.

previous studies (Table 3).[33]

The measurements of the blood pressure (systolic and diastolic and MAP) were highly predictive of subsequent development of PIH in this study and other reports in literature.[34]

Twenty-two cases (15.7%) in this study developed later in the study PIH 9.9% of the low risk group of xases developed PIH while 26.5% of the cases in the high-risk cases developed PIH. The difference incidences 11.8% & 19.3% the USA it was 7.6%.[35] The difference between these studies could be in the population or the study design or other factors.

The lipid profile was found to increase from the second to the third trimester in both groups but the increase in the high-risk group was significantly more in the high-risk group than the low risk group (Table 6). This agrees with some results [37] and disagress with others.[24] This highlights the predictive ability of the lipid profile in predicting the future development of PIH is high-risk cases.

The lipid profile includes serum cholesterol, triglycerides, HDL, LDL, VLDL (Table 10).

The resistance index shows a statistically significant difference in both groups in right and left uterine arteries.

Pulsatility index shows no statistically significant difference among low and high-risk group ($p>0.05$) in both visits on the right uterine artery. But it is significantly higher in high-risk group compared to low risk group. This agrees with many researchers.[38] The PI nearly doubles in the high-risk group. There is an obvious increase in left uterine artery RI in PIH group compared to normal as. There is strong statistical difference between two groups. (Table 7)

The mean value of systolic/diastolic ratio in right uterine artery of normal group was one third that of the high-risk group the difference is strongly sighificant. In normal pregnancy, this S/D ratio and other indices of pulsatility progressively decline until the 26th week of pregnancy after which no further decline is noted.[27]

In the high-risk group, abnormal Doppler indices could efficiently predict cases with complicated pregnancy PIH who were at high risk.

All Doppler indices were correlated strongly with lipid profile values in cases which developed PIH in the second visit were significantly having high lipid profile values. (Table 11)

There is an agreement with our results concerning serum cholesterol level and high density lipoprotein cholesterol as their linear changes in both associated with changes in both diastolic and systolic pressure from the start to late second trimester. Our results are in agreement with a previous study that there is a relation between serum lipids in early pregnancy and the development of PIH.[25]

These observations, taken together with those made from a number of cross-sectional studies of maternal lipid status in pre-eclamptic and normotensive pregnant women, point to the involvement of abnormal lipid metabolism in the pathogenesis of pre-eclampsia.1[2,39,40]

Endothelial cell dysfunction, resulting from placental under-perfusion, is considered to play a pivotal role in the pathogenesis of pre-eclampsia.[41]

Investigators have proposed that poor placental perfusion, due to abnormal placental trophoblast implantation gives rise to blood-borne products that may activate endothelial cells.[12,41]

Factors identified as endothelial cell activators include lipid peroxides,[2,42] cytokines[43,44] free fatty acids,[45] insulin, and circulating plasma lipids.[39]

Postulated biological mechanisms for the observed positive association between elevated maternal plasma lipids and lipoproteins with pre-eclampsia risk has been the subject of several recent reviews.[46,47] Observations made from studies of animals and humans with genetically determined or acquired hyperlipidemias suggest that lipids can damage the kidney and result in glomerulosclerosis.[40] Pre-eclampsia is associated with morphological changes in renal endothelial and mesangial cells. [40,41] In pre-eclampsia, these cells have been noted to be enlarged due to their engorgement with lipids.[40] These lipid-induced changes have recently been named 'glomerular histopathological endotheliosis'.[48]

Arbogast and Taylor[46] have postulated that the atherogenesies evident in placental spiral arteries taken from pre-eclamptics is suggestive of multiple cell cycles of cell death and re-endothelialization. Intracellular lipid accumulation in vascular and kidney endothelial cells is well established.[49] Endothelial cell activation or injury has been shown to indirectly and directly lead to activation of leukocytes and platelets, and the formation of lipid-laden foam cells.[46] High VLDL cholesterol exposure results in a thrombogenic cascade of events where marcophages, leukocytes and activated platelets trigger an inflammatory response - further inviting cytokines and adhesion molecule activation. Taken together, these observations are consistent with the thesis that elevations of maternal circulating lipids may play some role in poor placental implantation and/or reductions in placental perfusion very early in pregnancy.

Moveover other authors have hypothesized that defective placentation (resulting from lipid- or non-lipid-related causes), leading to placental hypoxemia may initiate a cascade of events including excessive lipid peroxidation in placental tissue.[49] Elevated circulating levels of lipid peroxides[12,42] as well as increased placental production of lipid peroxides have been well documented [12,42] in pre-eclamptic pregnancies. A reduction in prostacyclin synthesis, secondary to endothelial cell damage due to elevated lipid peroxidation, in conjunction with elevated synthesis of thromboxane by activated platelets may represent yet another possible biological mechanism

for the abnormal lipid metabolism and pre-eclampsia. An imbalance in the biosynthesis of thromboxane and prostacyclin (favoring vasoconstriction) has been documented in prospective studies of pre-eclampsia,[47] HDL cholesterol deficiency has been shown to reduce prostacyclin synthesis in vitro.[45] Therefore, oxidative stress, secondary to excess lipids and lipoproteins may bring about vasoconstriction. Constriction of placental vasculature, as a result of lipid-induced endothelial cell dysfunction, may lead to further increase in lipid peroxidation, thus worsening placental hypoxemia and perhaps contributing directly and/or indirectly to the hypertension seen in pregnant women.

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