Risk Factors and Impacts of Pre-Eclampsia: An Epidemiological Study among Pregnant Mothers in Cairo, Egypt

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Abstract: Introduction: Pre-eclampsia (PE) represents a major cause of morbidity and mortality in mother, fetus and infant in many parts of the world. Objectives: The aim of this study was to investigate the role of behavioral, socio-demographic and clinical conditions as risk factors of PE among pregnant mothers and to define the impact of PE on health of the fetuses and neonates. Subjects and methods: A case-control, hospital based study design was used. All cases and controls were interviewed and examined; clinically and laboratory. Results: Multiple gestations, rural residence, mothers married more than once, inter pregnancies' interval <3 years, primi-gravida, low social level and maternal age group 26-30 years were significant socio-demographic and personal risk factors (OR=9.79, 4.16, 4.0, 2.73, 2.16, 2.16 and 1.98, respectively). Further, much salty diet intake, no adequate fresh fruits/vegetables and much fat were significant dietary risk factors (OR=1.99, 1.85 and 1.83, respectively). Also; urinary tract infection, vaginal infection/vaginosis, asymptomatic bacteriuria, polyhydraminos, diabetes and stress were significant medical and obstetric/gynecologic risk factors (OR=5.59, 4.41, 3.62, 3.59, 3.35 and 2.98, respectively). Fetal growth restriction, preterm labor, neonate birth weight <2.5 kg and neonate intensive care admission were more common in pre-eclamptic mothers compared to controls with statistically significant differences (P=0.00, 0.04, 0.03 and 0.02, respectively). The mean of 1- and 5-minutes Apgar scores were significantly lower in newborns of pre-eclamptic mothers compared to controls (P=0.00 for each of them). Also, the mean Hb level was significantly lower in newborns of PE cases compared to controls (P=0.00). Recommendations: Improving ante-natal care for pregnant mothers in Egypt. Population based studies are needed in different areas in Egypt and on large numbers of mothers to understand the full epidemiology of pre-eclampsia.
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1. Introduction

Pre-eclampsia (PE) is a major complication of pregnancy. It is pregnancy-specific condition, which usually occurs after 20 weeks of gestation and resolves with delivery (Roberts, 1998). It is determined clinically by identification of pregnancy induced hypertension, proteinuria or generalized edema or both. PE may be mild or severe (Cunningham et al., 2010). The prevalence of PE has not changed during the last century (Hauth and Cunningham, 1999). The prevalence is varying according to the difference in classifications, definitions and the fact that many estimates are hospital basis. However, the prevalence is commonly cited to be about 7.0 % of first pregnancies (Roberts, 1998). The prevalence of hypertension observed at deliveries is approximately 10.0% that diagnosed with pregnancy- induced or aggravated hypertension (Brown et al., 2000). In Egypt, the prevalence of PE is 10.7% in a community based study (Gadalla et al., 1986). While, in hospital based studies it ranged from 9.1% (Mahaba et al., 2001b) to 12.5% (El-Houseinie et al., 1994) of all deliveries.

Pre-eclampsia is a disease with worldwide significance to mothers and infants; it may have health hazards that increase maternal, fetal and infant morbidity and mortality (Roberts, 1998 and Roberts et al., 2003a). Its greatest impact is in developing countries, where it accounts for 20.0-80.0% of the strikingly increased maternal mortality. While, in developed countries PE has a major effect on the fetus and neonate. Application of proper ante-natal care (ANC) and management has largely eliminated maternal mortality, frequently at the cost of preterm delivery. About 10.0% of PE cases occur at a stage of gestation where delivery exchanges a sick fetus in uterus for a sick premature infant in the nursery (Goldenberg and Rouse, 1998). Also, PE has associated with a higher risk for intra uterine growth restriction (IUGR), cerebral palsy (Report the Task Force ACOG/AAP, 2003) and persistent pulmonary hypertension of the newborn (Hernández-Díaz et al., 2007). Further, PE is a leading cause of perinatal mortality, 7.6% (Gaym, 2000). In developed countries perinatal mortality of infants of pre-eclamptic mothers is 5-fold greater than non pre-eclamptics. Further, about 15.0% of preterm births are indicated premature deliveries of PE (Goldenberg and Rouse, 1998). Moreover, PE can progress rapidly, putting both mother

and fetus at severe risk if no action is taken (Basso et al., 2006).

PE has been described as a "disease of theories" as the cause is not known. Some theories include rejection phenomenon (insufficient production of blocking antibodies), compromised placental perfusion, altered vascular reactivity, uterine muscle stretch (ischemia), dietary factors and genetic factors. None of these theories has been conclusively proved (Roberts & Cooper, 2001; Roberts & Lain, 2002 and Solmon & Seely, 2004).

Pregnancy induces increased venous capacitance, reduced systemic arterial resistance, and vasodilatation associated with a 50.0% increase in circulating blood volume (Marshall and Carpenter, 2007). PE is hypothesized to be a two-stage disorder with maternal-fetal interactions necessary to link the two stages (Roberts and Cooper, 2001). Reduced placental perfusion, secondary to abnormal implantation and subsequent reduced placental vascularization, is thought of as the first stage. The second stage; the maternal syndrome, develops in a subgroup of women with certain genetic, environmental, and/or behavioral risk factors (Roberts and Cooper, 2001) as a response to agents produced by the poorly perfused placenta (Roberts and Hubel, 1999). In a suitable maternal environment, endothelial dysfunction results (Roberts and Hubel, 1999) and initiates the coagulation cascade and ensuing multi-system sequelae (Surratt, 1993), stage 2 of PE (Bodnar et al., 2006).

Age, parity (Funai et al., 2005), low social status (MacGillivary, 1983), race, environmental factors (Cunningham et al., 2010), and genetic and familial predisposition influence the incidence of PE (Skjaerven et al., 2005). Also, increase inter-pregnancies space (Lie et al., 1998), multiple gestation (Sibai et al., 2000), nutrition deficiencies (Roberts et al., 2003b), obesity (Ros et al., 1998 and Roberts & Cooper, 2001), diabetes (Wolf et al., 2002 and Funai et al., 2005), infection and inflammatory processes (López-Jaramillo et al., 2001) and paternal factors (Li and Wi, 2000) are susceptible risk factors of pre-eclampsia.

Study Objectives

A- Ultimate objective:

Improve quality of the health of mother, fetus and infant in Egypt.

B- Immediate objectives:

1- To investigate the role of socio-demographic, behavioral and clinical conditions as risk factors of PE among pregnant mothers in Cairo, Egypt.

2- To determine the impact of PE on the health of the fetuses and neonates of the pregnant mothers in Cairo, Egypt.

2. Subjects and Methods

I- Study Questions:

Is there PE socio-demographic, behavioral and clinical risk factors? Is there PE health hazards on the fetuses and neonates?

II- Study Design:

A case-control, hospital based study design was used to investigate the current research problem.

III- Study Setting:

This study was conducted in the Obstetrics and Gynecology Department in Al-Hussein Hospital, Al-Azhar University.

IV- Study Sample:

According to sample size equation the sample was 86 cases, and to guard against sample size bias we increased the sample to be 100 PE cases. So, all the cases of PE attending the Obstetrics and Gynecology Department in Al-Hussein Hospital, Al-Azhar University were included in the study till sample reached the required number; 100. For each pre-eclamptic patient a healthy pregnant woman was chosen randomly. So, a control group of 100 healthy pregnant women was recruited.

All patients must be fulfilling the following inclusion criteria: 1) Age of patients up to 30 years, 2) Gestational age ≥33 weeks, 3) Have a definite specific diagnosis of PE. Also, all patients recruited in this study have fulfilled the following specific exclusion criteria: 1) Essential hypertension, 2) Pregnancy induced hypertension without proteinuria, 3) Intake of vitamins/antioxidants during the current pregnancy, 4) Blood diseases, 5) Kidney disease, 6) Liver disease, 7) Intrauterine fetal death, and 8) Ante-partum hemorrhage.

The controls enrolled in the study have fulfilled the following inclusion criteria: 1) Age up to 30 years, 2) Have no history of PE in the current or previous pregnancy, and 3) Gestational age ≥33 weeks. Also, the controls have fulfilled the same specific exclusion criteria used for the patients group.

V- Ethical Considerations:

The purpose of the study and procedures to be performed were explained to the cases and controls, an oral consent to participate in the study was taken accordingly. All patients were managed properly to control PE. All the cases and controls were delivered spontaneously in the normal vertex position or by Caesarian section according to the condition of each case.

VI- Study Tools and Methods:

1- Interview questionnaire:

It was used to collect data relevant to topic of the study. The patients and controls were submitted to an interview.

2- Diagnosis of PE: All patients must be fulfilling the following inclusion criteria: 1) Hypertension: Blood pressure (BP) ≥140/90 mmHg (Cunningham et al., 2010), 2) Proteinuria: Trace or more by dipstick method. Two random midstream urine specimens, collected ≥4 hours apart taken from each woman to avoid error due to false positive test, were used. The two results must be positive, so the diagnosis of proteinuria was significant (MacGillivary, 1983), and 3) Bilateral, pathological (≥+1) and not just dependant, lower limb edema. Edema is a common feature of pregnancy. But, edema of PE usually involves the face and hands, and persists (Cunningham et al., 2010).

3- Clinical examinations: Both general and local physical examinations were done for the cases and controls. Also, pelvi-abdominal ultra-sonography examination was done for both groups to estimate gestational age, to determine multiple fetuses, polyhydramnios and to detect fetal IUGR. Anthropometric measurements of mothers; height and weight were done. Weight (kg) was measured while women wear light outer garment and without shoes. Height (cm) was measured in standing position. Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). BMI classifications considered obese subject to be ≥30 kg/m² (WHO, 2000).

All the neonates were evaluated clinically and their Apgar scores at 1- and 5-minutes were defined immediately after birth, low 5-minutes Apgar (activity, pulse, grimace, appearance and respiration) score was considered <4 (Casey et al., 2001). Also, weight (kg) by a special pediatric scale was done immediately at birth.

4- Laboratory investigations: Laboratory examinations were done for all cases and controls. Midstream urine samples were taken at time of interviewing the cases and controls for microscopic examination to detect cases of urinary tract infections that may be symptomatic or not. Also, umbilical vein blood samples were taken from all neonates of the cases and controls at birth to determine their hemoglobin (Hb) concentration level (g/dl) by using Drabkin's photometric method.

VII- Statistical Analysis:

Odds ratio (OR) with 95% confidence interval (CI) or exact confidence limits (ECL), t-student test, Yates corrected Chi-square (χ^2) and 2-tailed Fisher exact (FE) were used as tests of significance. The significance level for t, χ^2 and FE was accepted if the P-value <0.05.

3. Results

As regard socio-demographic risk factors of the PE cases and controls (table 1), low educational level (illiterates, and read and write) of the cases was insignificant risk factor (OR=1.51, 95% CI: 0.83-2.75). The house wives occupation and the unskilled workers are insignificant risk factors (OR=1.44, 95% CI: 0.79-2.60 and OR=1.16, 0.60-2.22). Collectively, 59.0% of the patients were belonged to lower social level and represented a significant risk factor (OR=2.16, 95% CI: 1.18-3.95). Further, rural residence represents a significant risk factor for PE (OR=4.16, 95% ECL: 1.52-13.16). On the other hand, middle social level and urban residence are significant protective factors.

With respect to personal risk factors of the PE cases and controls (table 2), the young (18-21 year) and old (26-30 year) age groups are significant risk factors (OR=2.01, 95.0% CI: 1.00-4.06 and OR=1.98, 95.0% CI: 1.04-3.76, respectively). Also, less than one year marriage-pregnancy interval is significant risk factor (OR=1.84, 95% CI: 1.01-3.35). At the same time, primigravida is significant risk factor (OR=2.16, 95% CI: 1.18-3.96). Regarding inter-pregnancy space, more than 3 years is significant risk factor (OR=2.73, 95% CI: 1.08-7.01). Also, multiple gestations represented a significant risk factor (OR=9.79, 95% ECL: 1.30-433.39). Further, history of prior PE/eclampsia and abortion in first trimester are insignificant risk factors (OR=2.85, 95% ECL: 0.66-14.12 and OR=1.25, 955 CI: 0.45-3.47, respectively). Also, positive maternal family history of PE is insignificant risk factor (OR=4.85, 95% ECL: 0.96-46.94). Regarding change in husbands, marriage more than once is significant risk factor (OR=4.0, 95% ECL: 1.01-22.88).

Regarding life-style and behavioral risk factors of the PE cases and controls (table 3), absence of ante-natal care is insignificant risk factor (OR=1.36, 95% CI: 0.73-2.53). Also, physical activity is insignificant risk factor (OR=1.34, 95% CI: 0.73-2.47). Further, smoking during pregnancy is insignificant protective factor (OR= 0.49, 95% ECL: 0.01-9.68). Regarding diet intake, no adequate intake of fresh fruits and vegetables (OR=1.85, 95% CI: 1.01-3.39), much intake of fats (OR=1.83, 95% CI: 1.01-3.34) and much intake of salty diet (OR=1.99, 95% CI: 1.02-3.91) are significant risk factors. On the other hand, much intake of sugar (OR=1.51, 95% CI: 0.80-2.86) and no adequate intake of proteins (OR=1.35, 95% CI: 0.73-2.50) are insignificant risk factors.

With respect to medical, gynecological and obstetric risk factors among the PE cases and controls (table 4), obesity (OR=2.02, 95% CI: 1.05-3.90), stress (OR=2.98, 95% ECL: 1.04-9.70), diabetes (OR=3.35, 95% ECL: 1.09-12.23), urinary tract infection (OR=3.59, 95.0% ECL: 1.05-15.58), polyhydraminos (OR=3.59, 95% ECL: 1.05-15.58), asymptomatic bacteriuria (OR=3.62, 95% ECL: 1.19-13.10) and vaginal infection/bacterial vaginosis (OR=4.41, 95% ECL: 1.13-24.97) are significant risk factors.

As regard impacts of PE (table 5), 29.4% of the fetuses of pre-eclamptic women had IUGR compared to 5.9% of the controls (P=0.0002). At the same time, 8.0% of the cases had preterm labor compared to 1.0% of the controls (P=0.04). Moreover, 11.9% of the neonates were <2.5 kg at birth compared to 3.0% of the neonatal controls (P=0.03). Also, 12.8% of the neonates were admitted to neonatal intensive care units compared to 3.0% of the neonatal controls (P=0.02). Further, one (0.9%) of the neonates died during the first week of life compared to none of the neonatal controls (P=1.00). Also, 1- and 5-minutes Apgar scores of the neonates of patients and controls were 4.62±1.37, 6.16±1.09 and 6.41±1.88, 8.89±1.32, respectively with a statistically significant difference (P=0.00 for each of them). Lastly, levels of hemoglobin of the neonates of patients and controls were 14.12±5.23 and 18.22±5.74 g/dl, respectively with a statistically significant difference (P=0.00).

Table (1): Distribution of pre-eclampsia (PE) cases and control group according to socio-demographic risk factors.

Socio-demographic risk factors	PE cases (n=100)		Control group (n=100)		OR (95% CI) OR (95% ECL)*
	No.	%	No.	%	
Educational status:					
Illiterate, read and write	48	48.0	38	38.0	1.51 (0.83-2.75)
Elementary	39	39.0	47	47.0	0.72 (0.40-1.31)
Secondary and university	13	13.0	15	15.0	0.85 (0.35-2.02)
Occupational status:					
House wife	56	56.0	47	47.0	1.44 (0.79-2.60)
Unskilled	31	31.0	28	28.0	1.16 (0.60-2.22)
Semi-skilled & skilled	9	9.0	19	19.0	0.42 (0.17-1.05)
Professional	4	4.0	6	6.0	0.65 (0.13-2.86)*
Social level:					
Low	59	59.0	40	40.0	2.16 (1.18-3.95)
Middle	33	33.0	49	49.0	0.51 (0.28-0.94)
High	8	8.0	11	11.0	0.70 (0.24-2.00)
Residence:					
Rural	21	21.0	6	6.0	4.16 (1.52-13.16)*
Urban	79	79.0	94	94.0	0.24 (0.08-0.66)*

Table (2): Distribution of pre-eclampsia (PE) cases and control group according to personal risk factors.

Personal and clinical risk factors	PE cases (n=100)		Control group (n=100)		OR (95% CI) OR (95% ECL)*
	No.	%	No.	%	
Mother's age:					
18-21	32	32.0	19	19.0	2.01 (1.00-4.06)
22-25	27	27.0	55	55.0	0.30 (0.16-0.57)
26-30	41	41.0	26	26.0	1.98 (1.04-3.76)
Marriage-pregnancy interval:					
<12 months	54	54.0	39	39.0	1.84 (1.01-3.35)
≥12 months	46	46.0	61	61.0	0.54 (0.30-0.99)
Parity:					
Primi	58	58.0	39	39.0	2.16 (1.18-3.96)
Multi	42	42.0	61	61.0	0.46 (0.25-0.85)
Inter pregnancies' interval:	(n=42)		(n=61)		
≤3 Years	11	26.2	30	49.2	0.37 (0.14-0.93)
>3 Years	31	73.8	31	50.8	2.73 (1.08-7.01)
Multiple gestations:					
Yes	9	9.0	1	1.0	9.79 (1.30-433.39)*
No	91	91.0	99	99.0	0.10 (0.00-0.77)*
History of prior PE/eclampsia:	(n=42)		(n=61)		
Yes	7	16.7	4	3.3	2.85 (0.66-14.12)*
No	35	83.3	57	96.7	0.35 (0.07-1.51)*
History of prior abortion:					
Yes:	17	17.0	21	21.0	0.77 (0.36-1.66)
1st trimester	11	11.0	9	9.0	1.25 (0.45-3.47)
2nd trimester	6	6.0	12	12.0	0.47 (0.14-1.42)*
Maternal family history of PE/E:					
Yes:	9	9.0	2	2.0	4.85 (0.96-46.94)*
Mother (any pregnancy)	7	7.0	1	1.0	7.45 (0.92-339.15)*
Mother (in her own pregnancy)	5	5.0	0	0.0	Undefined
Sisters	2	2.0	1	1.0	2.02 (0.10-120.38)*
Married more than once:					
Yes	11	11	3	3.0	4.0 (1.01-22.88)*
No	89	89.0	97	97.0	0.25 (0.04-0.99)*

Table (3): Distribution of pre-eclampsia (PE) cases and control group according to life-style and behavioral risk factors.

Life-style and behavioral risk factors	PE cases (n=100)		Control group (n=100)		OR (95% CI) OR (95% ECL)*
	No.	%	No.	%	
Ante-natal care (ANC):					
No:	68	68.0	61	61.0	1.36 (0.73-2.53)
Yes:	32	32.0	39	39.0	0.74 (0.39-1.37)
Regular ANC:					
Yes	14	14.0	19	19.0	0.82 (0.29-2.32)
No	18	18.0	20	20.0	1.22 (0.43-3.48)
Time of ANC:					
Early (<20 weeks of gestation)	13	13.0	21	21.0	0.59 (0.20-1.67)
Late (>20 weeks of gestation)	19	19.0	18	18.0	1.71 (0.60-4.91)
Physical activity:					
Yes	64	64.0	57	57.0	1.34 (0.73-2.47)
No	36	36.0	43	43.0	0.75 (0.41-1.37)
Smoking:					
No	99	99.0	98	98.0	2.02 (0.10-120.38)*
Yes	1	1.0	2	2.0	0.49 (0.01-9.68)*
Diet intake:					
No adequate fresh fruits/vegetables	64	64.0	49	49.0	1.85 (1.01-3.39)
Much fat intake	57	57.0	42	42.0	1.83 (1.01-3.34)
Much sugar intake	72	72.0	63	63.0	1.51 (0.80-2.86)
No adequate protein	66	66.0	59	59.0	1.35 (0.73-2.50)
Much salty diet intake	78	78.0	64	64.0	1.99 (1.02-3.91)

Table (4): Distribution of pre-eclampsia (PE) cases and control group according to medical, gynecological and obstetric risk factors.

Medical, gynecological and obstetric risk factors	PE cases (n=100)		Control group (n=100)		OR (95% CI) OR (95% ECL)*
	No.	%	No.	%	
Medical :					
Obesity (BMI≥30 kg/m²)	76	76.0	61	61.0	2.02 (1.05-3.90)
Diabetes mellitus	15	15.0	5	5.0	3.35 (1.09-12.23)*
Asymptomatic bacteriuria	16	16.0	5	5.0	3.62 (1.19-13.10)*
Urinary tract infection	13	13.0	4	4.0	3.59 (1.05-15.58)*
Stress	16	16.0	6	6.0	2.98 (1.04-9.70)*
Obstetric/gynecologic:					
Polyhydramnios	13	13.0	4	4.0	3.59 (1.05-15.58)*
Vaginal infection/vaginosis	12	12.0	3	3.0	4.41 (1.13-24.97)*

Table (5): Distribution of neonates of the pre-eclampsia (PE) cases and control group according to disease impacts.

Fetal and neonatal impacts of PE	PE cases (n=109)		Control group (n=101)		Yates χ^2 t- value*	P-value
	No.	%	No.	%		
Fetal growth restriction:						
Yes	32	29.4	6	5.9	17.85	0.0002
Preterm labor (n=100):						
Yes	8	8.0	1	1.0	FE: P-value= 0.04	
Birth weight						
<2.5 kg	13	11.9	3	3.0		
≥2.5 kg	96	88.1	98	97.0	4.77	0.03
Neonatal intensive care admission:						
Yes	14	12.8	3	3.0	5.61	0.02
Perinatal deaths:						
Yes	1	0.9	0	0.0	FE: P-value= 1.00	
1-minute Apgar score	4.62±1.37		6.16±1.09		-9.046*	0.000
5-minutes Apgar score	6.41±1.88		8.89±1.32		- 11.127*	0.000
Hb (g/dl)	14.12±5.23		18.22±5.74		- 5.397*	0.000

4. Discussion

PE results from the interaction between economic, psycho-social, nutritional, environmental and genetic factors (López-Jaramillo et al., 2001).

PE being more common in poor women long ago, numerous conflicting hypotheses were advanced (Roberts et al., 2003a). Further, there is a high rate of PE in developing countries (Caughey et al., 2005). Lower education level attainment reduces access to medical care for screening and is often associated with greater exposure to poor nutrition, physical inactivity, being overweight and other risk factors (Howard et al., 1992). In Egypt, 32.0% of the PE cases were illiterates compared to 26.0% of the controls, and 28.0% of the cases had up to secondary education compared to 34.0% of the controls, but the differences were insignificant (Mahaba et al., 2001a). Further, PE incidence was higher among manual workers (Baired, 1969). On the other hand, there was no significant difference between PE cases and controls regarding housewives and employees (P=1.0) (Ziaei et al., 2008). Also, In Egypt PE was found among 16.0% and 5.0% of rural and urban pregnant residents, respectively (Gadalla et al., 1986). Collectively, lower socioeconomic class is reported to have a higher incidence of PE. Poor ante-natal care, improper nutrition and increased incidence of concealed pregnancies are confounding factors. Also, the increased in the incidence of severe PE in very young girls may reflect the greater tendency to social neglect among this group. Further, reports on PE during war, famine and drought refer to the effects of war on the incidence of PE during the two major World Wars; higher incidence of PE/eclampsia was reported in Germany. Also, there is probably a difference in the incidence of PE among racial groups; its incidence in white races is 6.2%, while it is 8.5% in black race. This variation is mostly due to genetic factor that relates underlying chronic hypertension (MacGillivary, 1983). The differences between races may reflect the differences in genetic, nutritional, environmental and socioeconomic state.

There is a J-shaped curve for relationship between maternal age and the incidence of PE with a slightly increased pattern among young pregnant and a markedly increased incidence among the older ones, more than 35 years (MacGillivary, 1983 and Rosalia et al., 1998). So, advanced age is common risk factor for PE (Duckitt and Harrington, 2005). Also, the incidence of severe PE is more in pregnant teen aged girls. However, it remains uncertain whether this truly an increased in the incidence of severe PE in very young girls, or whether it is a reflection of the greater tendency to social neglect among them (MacGillivary, 1983). In young primigravida the increase incidence of PE may be due to poor immune capacity at young age, while increased incidence with increasing age may probably reflect the increasing incidence of essential or latent essential hypertension (Davey, 1995). Further, women over 40 had a three-fold increased incidence of hypertension compared to control women aged 20-30 years (MacGillivary, 1983). On the other hand, some studies didn't found significant age difference between PE cases and controls (Caughey et al., 2005; Lou et al., 2008; Kolusari et al., 2008, and Ziaei et al., 2008).

At the same time, the length of sexual relation is inversely related to the incidence of PE, a sexual relationship of less than 4 months comparing to a sexual relationship of at least 12 months is associated with a 7-fold increased risk of development of PE (Wang, 2003). Also, PE is more common in women implanted with an oocyte fertilized with surgically obtained sperm rather than their partner's ejaculated sperm (Wang et al., 2002). These data suggest that the protective effect of semen exposure on the later development of PE is associated with exposure to sperm cells, or a factor closely linked with sperm in the ejaculate (Wang et al., 2002 and Wang, 2003). PE has been regarded as a disease of primigravidae, and it is suggested that a previous pregnancy is protective against the development of PE (Campbell and MacGillivary, 1985). Studies observed that the combination of primigravidity and age over 35 years leads to a much higher risk of developing PE (Campell et al., 1985). Also, our result is consistent with Mahaba et al. (2001a); they reported that 70.0% of their pre-eclamptic cases were primigravidae. Further, the risk of PE in a second pregnancy increases with maternal age, 1.3/5 years of increased age (Lie et al., 1998).

The risk of PE is increased in circumstances where formation of blocking antibodies to antigenic sites on the placenta might be impaired. This may arise where immunization by previous pregnancy is lacking as in first pregnancies (Cunningham et al., 2010). Major support for this hypothesis comes from studies that show the protective effect of sperm exposure (Dekker et al., 1998). Also, the risk of PE in a second pregnancy increases with interval between pregnancies, 1.5/5 years interval between first and second pregnancies (Lie et al., 1998 and Skjaerven et al., 2002). Also, PE is more frequent in multiple pregnancies (Sibai et al., 2000). Induced and spontaneous abortions are reported to be associated with decreased risks of PE (Eras et al., 2002). In details, prior abortion in the second trimester was found to be protective against PE, but prior first trimester abortion was risk factor (Campbell and MacGillivary, 1985). Also, about 1/3 of women who have had eclampsia in their first pregnancy developed PE in a later pregnancy; the prevalence of chronic

hypertension in these women with recurrent PE is high (Sibai et al., 1987).

Susceptibility to PE is highly heritable. Population based studies have shown a strong familial tendency to PE (Cooper et al., 1993). The single gene hypothesis fits with PE, but multi-factorial inheritance can't be excluded (Chesley and Cooper, 1986). Also, maternal predisposition to PE has been reported (Esplin et al., 2001; Nilsson et al., 2004 and Skjaerven et al., 2005). It seems reasonable to attribute patterns of familial predisposition to genetic inheritance. Daughters born after a pre-eclamptic pregnancy may carry their mothers' susceptibility genes, as well as genes from either parent that operate through the fetus (Lie et al., 1998 and Esplin et al., 2001). The proportion of preterm PE was 10.0% in the parents and 22.0% in the offspring. Women who were born after a pre-eclamptic pregnancy had more than twice the risk of having PE in their first pregnancy (OR=2.2, 95% CI: 2.0-2.4), and still had the same risk (OR=2.3, 95% CI: 1.8-2.9) of PE in their second birth compared to other women. Further, sisters who were not themselves born after a pregnancy complicated by PE were at increased risk of PE compared to women with no family history of PE (OR=2.0, 95% CI: 1.7-2.3). Also, women born after pre-eclamptic pregnancies were more likely to trigger severe PE in their own pregnancy (OR=3.0, 95% CI: 2.4-3.7) (Skjaerven et al., 2005). However, we cannot exclude potential confounding by other risk factors. But, a stronger familial association for clinically severe PE than for mild was found (Vatten et al., 2004). Further, maternal genes and fetal genes from either the mother or father may trigger PE. The maternal association is stronger than the fetal association. The familial association predicts more severe PE (Skjaerven et al., 2005). Also, change of partner between births has been associated with the risk of PE (Cnattingius et al., 1997 and Skjaerven et al., 2002). Major support for this hypothesis comes from epidemiological studies that show the impact of a change in partners, and the increased frequency of PE after donor insemination and oocyte donation (Dekker et al., 1998). Men who fathered a pre-eclamptic pregnancy were nearly twice as likely to father a pre-eclamptic pregnancy in a different woman, regardless of whether she had already had a pre-eclamptic pregnancy or not (Lie et al., 1998). Also, among women with two consecutive births; women without PE/eclampsia in the first birth, changing partners resulted in a 30.0% increase in the risk of PE/eclampsia in the subsequent pregnancy compared to those who didn't change partners. While, among women with PE/eclampsia in the first birth, changing partners resulted in a 30.0% reduction in the risk of PE/eclampsia in the subsequent pregnancy. The difference of changing paternity effect on PE/eclampsia risk between women with and without a history of PE/eclampsia was significant. These findings support the hypothesis that parental human leukocyte antigen sharing may play a role in the etiology of PE/eclampsia (Li and Wi, 2000).

Poor ante-natal care is risk factor for PE (MacGillivary, 1983). But, in this work poor ante-natal care is insignificant risk factor. PE is not a common cultural concept among most of the mothers in Egypt, more than half of our cases were belong to low social level. Also, physical inactivity might be risk factor for PE (Howard et al., 1992). Evidence suggests that physically active women are less likely to develop PE. Regular exercise resulted intracellular and extracellular conditions that should counteract the enhancement of oxidative stress, thus interfering with the process leading to endothelial dysfunction (Yeo and Davidge, 2001). On the other hand, bed-rest has been successfully used as effective method of treating hypertensive disorders of pregnancy. Also, there have been many reports that the incidence of PE is lower among smokers than among nonsmokers (Cnattingius et al., 1997 and Conde-Agudelo et al., 1999). So, smoking during pregnancy is protective (Conde-Agudelo et al., 1999). The incidence of PE in cigarette smokers is about 50.0% that in non-smokers. This is due to the presence of hypotensive agents as thiocyanate in tobacco (Darby and Wilson, 2002). However, this benefit is cancelled out by the substantial negative effect of smoking on fetal growth, risk for placental abruption, general health hazards and increases the incidence of fetal mortality (WHO, 1987 and Cnattingius et al., 1997). Marriage may serve as partial proxies for mothers' smoking, as married had a higher risk of PE (possibly reflecting a lower prevalence of smoking) than non married was negatively associated with PE (Basso et al., 2006).

Nutrition has long been hypothesized to have a role in the etiology of PE. The hypotheses have been diverse and often mutually exclusive (MacGillivary, 1983). There are several reports showing that metabolic- and mineral level changes are associated with abnormalities of pregnancy (Adam et al., 2001). The incidence of PE is more common in poor women. This suggested that nutrients might be involved in the disorder. But, in many studies PE is poorly defined and nutritional data are obtained on women with PE (Roberts et al., 2003a). It is now well understood that, while PE is clinically evident late in pregnancy, the causal exposure(s) and many of the pathophysiologic changes are present months earlier. Periconceptional exposures may be particularly relevant, as they may affect implantation and/or decidual vascular remodeling (stage 1 of PE) (Bodnar et al., 2006). It is

indicated that women with PE had a lower intake of energy, protein and fats than did controls. However, further interrogation indicated that these differences occurred after the woman became ill and were considered to be secondary to the disease rather than causal (Davies et al., 1976). Excess intake of protein, calories, sugar and sodium is associated with onset of PE (Lauro et al., 1997). High intake of polyunsaturated fatty acids, energy and sucrose is associated with increased risk of PE (Clausen et al., 2001). Diet in the past year was assessed at delivery in women with and without PE. It was found that intakes of vitamin C, fruits and vegetables below recommended values were associated with increased risk of PE (Zhang et al., 2002). However, periconceptional and prenatal intakes were not assessed separately in this study, so it is difficult to discern during which time period low vitamin C, fruit and vegetable intakes were most relevant for the development of PE (Bodnar et al., 2006). Also, certain nutrients found in multivitamins, such as vitamin C and vitamin E, have been given in form of supplement, starting in mid pregnancy and have been reported to reduce the risk of PE (Chappell et al., 2002; Roberts et al., 2003a and Bodnar et al., 2006). Energy intake was higher in women with PE and highest in early onset PE. The main difference between cases and controls was an increased intake of sucrose-containing soft drinks (Clausen et al., 2001). Other study found no difference in the energy intake between cases and controls (Morris et al., 2001). Although the belief that low protein intake is associated with an increased risk of PE (Brewer, 1976), none of the studies indicated reduced protein intake in women with or destined to develop PE. This is supported by trials of protein supplementation that did not reduce the incidence of PE (Herrera et al., 1998 and Crowther et al., 1999). Collectively, women with well-defined PE were examined with a crude food frequency questionnaire and no gross nutritional differences were found (Atkinson et al., 1998).

In the present study several medical disorders such as obesity, diabetes, urinary tract infections…etc were found to be risk factors for PE. There is general agreement that the incidence of PE is higher in obese women (Sibai et al., 1997; Ros et al., 1998; Roberts & Cooper, 2001 and Skjaerven et al., 2005). So, elevated BMI is risk factor for PE (Duckitt and Harrington, 2005). Women with a greater BMI in pregnancy are more likely to become hypertensive than those with a lower BMI (Pipkin, 2001). The increase in PE over time may reflect increases in BMI in recent years (Midthjell et al., 1999). Weight of the PE patients and controls was 81.0±13.9 and 69.0±14.0 kg, respectively with a statistically significant difference (Mahaba et al., 2001a). Evidence suggests that the association with obesity may be limited to the relatively mild type of PE with term delivery (Odegard et al., 2000). Education may serve as partial proxies for obesity, because higher education, which may correlate with lower BMI, was negatively associated with PE (Basso et al., 2006). On the other hand, Lou et al. (2008) and Ziaei et al. (2008) didn't found significant BMI difference between PE cases and controls.

Diabetes is an important risk factor for PE (Ros et al., 1998; Roberts & Cooper, 2001 and Funai et al., 2005). In the present study we found that DM is risk factor for PE. PE has been frequently reported as a complication of gestational diabetes. But, the relationship between these two conditions is not well understood (Vambergue et al., 2002). Common risk factors, such as elevated BMI and advanced age have been noted for each of the two conditions (Duckitt and Harrington, 2005). Also, there might be underlying common pathophysiology; insulin resistance (Ostlund et al., 2004 and Scioscia et al., 2009), chronic inflammation (Borzychowski et al., 2006 and Scioscia et al., 2009) and endothelial dysfunction (Roberts and Gammill, 2006). Early insulin resistance is associated with late pregnancy PE (Wolf et al., 2002). There is a 5.0% increase in the incidence of PE in pregnant diabetics. Also, the increased incidence of PE could be partially explained by the poor control of the diabetes; and in some of the cases, there may have been underlying renal disease, rather than true PE (White, 1965).

A growing body of evidences link infections with PE (Sacks et al., 1998 and López-Jaramillo et al., 2001). Generalized inflammatory state is feature of PE. Maternal leukocytes and maternal endothelium are contributors (Raijmakers et al., 2004). The incidence of asymptomatic bacteriuria was higher in pregnant women with PE (19.0%) than in normal gravidas (3.0%-6.0%) (Hill et al., 1986). Also, the incidence of urinary tract infection in pre-eclamptic women was higher than in normal pregnant women (Hsu and Witter, 1995). Further, urinary tract infection was shown to be a strong risk factor for PE (OR=4.23, 95% CI: 1.05-5.09) (Abi-Said et al., 1995). During pregnancy, urinary tract infection was associated with nearly a 2-fold increased risk for PE. Further, primiparas who had a urinary tract infection were five times more likely to develop PE than those who did not have urinary tract infection during pregnancy (OR=5.3, 95% CI: 2.9-9.7) (Mittendorf et al., 1996). The role of infection in the pathogenesis of PE is particularly relevant in developing countries, where the high incidence of chronic sub-clinical infection may contribute to the high incidence of PE (López-Jaramillo et al., 2001). Further, pregnant women with

asymptomatic bacteriuria, and vaginal infections and bacterial vaginosis who were identified and treated had a 64.0% reduction in incidence of PE. This dramatic reduction was due to the early identification and principally treatment of asymptomatic infections. But, it is not possible to make a definitive statement that infection is the major risk factor for PE. It is proposed that chronic sub-clinical infections may increase maternal cytokines to levels high enough to affect vascular endothelial function in women with a predisposition to develop PE (Herrera et al., 2001).

Depression and anxiety in early pregnancy are associated with the risk for PE (Kurki et al., 2000). In the present study maternal strain might be a cause of PE. This was in accordance with MacGillivary (1983). PE is a state of sympathetic over activity, which reverts to normal after delivery. The increase in peripheral vascular resistance blood pressure (BP) in PE is mediated, partially, by a substantial increase in sympathetic vasoconstrictor activity (Roberts, 1998). High levels of stress can lead to a temporary but dramatic increase in BP (Tobe et al., 2005 and Mohammed, 2009). Further, if the subject try to relax by eating more or drinking alcohol, you may only fuel, problems with high BP (Tobe et al., 2005). If stress itself is a risk factor, it could be because chronic stress exposes to unhealthy, persistently elevated levels of stress hormones like adrenaline and cortisol (Murray and Pizzorno, 2006).

There might be an increased incidence of PE in polyhydramnios cases that may be due to the associated hyper-placentosis (Roberts, 1998 and Ros et al., 1998). There is a stimulation of nerve endings along smooth muscles of the wall of the uterus causing spasm of the renal artery. The subsequent renal ischemia led to proteinuria and activation of the rennin-angiotensin system thus leading to hypertension. Both hypertension and proteinuria result in edema of the different tissues (Hays and Smetter, 1986; Roberts, 1998 and Ros et al., 1998).

There are reports showing that metabolic- and mineral level changes associated with abnormalities of fetal growth (Adam et al., 2001). But, the major cause of fetal compromise in PE is reduced uteroplacental perfusion (Lindheimer et al., 1999). The intervention that effectively reverses PE is delivery (Meis et al., 1998). PE is associated with a significant risk for pregnancy unfavorable outcome including preterm birth, low birth weight and perinatal deaths (Nosseir et al., 1990 and El-Houseinie et al., 1994). Preterm delivery substantially increases the risk of neonatal death (Kramer et al., 2000). Collectively, the pregnancy unfavorable outcome may lead to the observed lower 1- and 5-minutes Apgar scores and level of Hb in the neonates of PE cases compared to controls' neonates. The association of PE with fetal IUGR is well known especially in pregnancies with early onset disease (El-Houseinie et al., 1994 and Xiong et al., 2000). Abnormal placenta is clearly involved in the genesis of both PE and fetal IUGR (Cross, 1996). It has been proposed that product(s) of the fetal-placental unit enter circulation and then initiate the maternal pathophysiologic changes of PE (Roberts et al., 1990). However, there is evidence that both feto-placental and maternal factors interact in manifesting endothelial cell dysfunction and its clinical manifestations (Taylor and Roberts, 1999). Preterm labor may occur spontaneously in cases of PE and eclampsia. However, it is more likely to be due to artificial induction (Ferris, 1990). Hypertensive pregnant patients have 3-4 times more preterm deliveries than did the normotensive women (Lin et al., 1982 and El-Houseinie et al., 1994). PE is a primary and important indication for preterm delivery in, especially, developed (Goldenberg and Rouse, 1998) and in developing (El-Houseinie et al., 1994; Kolusari et al., 2008 and Ziaei et al., 2008) countries, a trend encouraged in part by the increasing ability to manage extremely preterm infant in highly equipped neonatal intensive care units (Friedman et al., 1999). As expected infants of PE women were delivered earlier and, therefore, there was significant difference in birth weight of the neonates of PE patients compared to controls (2.26±0.91 vs. 3.22±0.41 Kg, $P<0.001$) (Kolusari et al., 2008). So, there is a significant increase in number of neonatal admission to intensive care units among the neonates of the PE group as a result of more preterm deliveries and a more prevalence of low birth weight babies (Ananth et al., 2005). Delivery exchanges a sick fetus for a sick premature infant (Goldenberg and Rouse, 1998). However, medically indicated preterm delivery may help prevent stillbirth (Ananth et al., 2005). But, the infant might then pay a high compensatory price in postnatal increased risk. Such risk could persist well beyond the neonatal period but be difficult to detect on a population level because of the overall declining trend in infant mortality (Basso et al., 2006). Also, PE is associated with 5-fold increase in perinatal mortality (Hauth and Cunningham, 1999). A large proportion of the perinatal mortality is consequently due to iatrogenic prematurity. Up to 15.0% of preterm births are a result of PE (Meis et al., 1998). Among pre-eclamptic pregnancies, inductions before 37 weeks increased from 8.0% in 1967-1978 to 20.0% in 1991-2003. During this 35 year, the risk of stillbirth decreased from 4.2 to 1.3 in PE compared to normal pregnancies. Also, the risk of neonatal death after pre-eclamptic pregnancy remained relatively stable, 1.7 vs. 2.0. Later infant and childhood mortality also showed little change. Fetal survival in pre-eclamptic

pregnancies has vastly improved over the past 35 years, presumably because of more aggressive management. However, the relative risk of neonatal death following a pre-eclamptic pregnancy has not changed over time. So, PE still carries a 2-fold increased risk of neonatal death (Basso et al., 2006). A review of clinical trials of delayed versus immediate delivery in fact suggested better outcomes with delayed delivery in well-selected patients (Friedman et al., 1999). So, when PE occurs early in pregnancy, even a few more days in uterus may be a key to a new born survival (Friedman et al., 1999 and Sibai, 2003). Also, as there is a paradoxical effect of smoking in pre-eclamptic women; smoking increases the rates of perinatal mortality, abruptio placentae and IUGR (Cnattingius et al., 1997). Further, PE is associated with a higher risk for cerebral palsy of the newborn (Report the Task Force ACOG/AAP, 2003), and it is associated with a higher risk for persistent pulmonary hypertension of the newborn (Hernández-Díaz et al., 2007). Also, 1- and 5-minutes Apgar scores of the neonates of PE patients were significantly lower than controls (Kolusari et al., 2008 and Ziaei et al., 2008).

Conclusions and Recommendations

PE risk factors can be manipulated, so primary preventive strategies are important. Good ante-natal care, screening, early detection and interventions for PE should be strengthened by all health team members. Also, limited information of health team members about maternal dietary intake as well as trace elements content of food consumed by this vulnerable group of population limited their ability to assess diet intake of the micro- and macro-nutrients and risk of PE. Further, early detection demands careful ante-natal care at appropriate intervals, especially in women predisposed to PE. Major risk factors are primipara, family history of PE, multiple fetuses, diabetes, urinary tract infection, low social level and obesity. Also, fetal IUGR, preterm labor, low birth weight and neonate intensive care admission were more common in PE. A program of bio-psycho-social risk assessment must be developed and added to standard ante-natal care. This allows identifying pregnant women at risk for PE, helps to define nutritional supplementation interventions to prevent PE, and to screen and treat asymptomatic urinary tract and cervical infections, thus reducing maternal and perinatal morbidity and mortality. We recommend improving ante-natal care, health education and conducting more population based studies on large number of pregnant women to understand the epidemiology of PE and its impacts on mother and her fetus and infant in Egypt.

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References

Abi-Said D, Annegers JF, Combs-Cantrell D, Frankowski RF and Willmore LJ (1995): Case-control study of the risk factors for preeclampsia. Am J Epidemiol, 142: 437-41.

Adam B, Malatyaliogu E, Alvur M and Talu C (2001): Magnesium, zinc and iron levels in pre-eclampsia. Maten Fetal Med, 10: 246-50.

Ananth CV, Joseph KS, Oyelese Y, Demissie K and Vintzileos AM (2005): Trends in preterm birth and perinatal mortality among singletons: United States, 1989 through 2000. Obst Gynecol, 105: 1084-91.

Atkinson JO, Mahomed K, Williams MA, Woelk GB, Mudzamiri S and Weiss NS (1998): Dietary risk factors for pre-eclampsia among women attending Harare Maternity Hospital, Zimbabwe. Cent Afr J Med, 44: 86-92.

Baired O (1969): Combined text book of obstetric and gynecology for students and practitioners. Edinburgh, London, Livingston, Ltd.

Basso O, Rasmussen S, Weinberg CR, Wilcox AJ, Irgens LM and Skjaerven R (2006): Trends in fetal and infant survival following preeclampsia. *JAMA,* 296: 1357-62.

Bodnar LM, Tang G, Ness RB, Harger G and Roberts JM (2006): Peri-conceptional multivitamin use reduces the risk of pre-eclampsia. Am J Epidemiol, 164(5): 470-7.

Borzychowski AM, Sargent IL and Redman CW (2006): Inflammation and pre-eclampsia. Semin Fetal Neonatal Med, 11: 309-16.

Brewer T (1976): Role of malnutrition in pre-eclampsia and eclampsia. Am J Obst Gynecol, 125: 281-2.

Brown MA, Hague WM, Higgins J, Lowe S, McCowan L, Oats J, Peek MJ, Rowan JA and Walters BN (2000): Australasian Society of the Study of Hypertension in Pregnancy. The detection, investigation and management of hypertension in pregnancy: Full consensus statement. Aust J Obst Gynecol, 40(2): 139-55.

Campbell DM and MacGillivary I (1985): Pre-eclampsia in second pregnancy. Br J Obst Gynecol, 3: 32-6.

Campbell DM, Pearce JMF and Hackett G (1985): Qualitative assessment of uteroplacental blood flow: Early screening test for high risk pregnancies. Obst Gynecol, 68: 649-53.

Casey BM, McIntire DD and Leveno KJ (2001): The continuing value of the Apgar score for the assessment of newborn infants. N Engl J Med, 344: 467-71.

Caughey AB, Stotland NE, Washington AE and Escobar GJ (2005): .Maternal ethnicity, paternal ethnicity and parental discordance: Predictors of preeclampsia. Obst Gynecol, 106: 156-61.

Chappell LC, Seed PT, Kelly FJ, Briley A, Hunt BJ, Charnock-Jones DS, Mallet A and Poston L (2002): Vitamin C and E supplementation in women at risk of pre-eclampsia is associated with changes in indices of oxidative stress and placental function. Am J Obst Gynecol, 187: 777-84.

Chesley LC and Cooper DW (1986): Genetics of hypertension in pregnancy: Possible single gene control of pre-eclampsia and eclampsia in the descendants of eclamptic women. Br J Obst Gynecol, 93: 898-908.

Clausen T, Slott M, Solvoll K, Drevon CA, Vollset SE and Henriksen T (2001): High intake of energy, sucrose and polyunsaturated fatty acids is associated with increased risk of pre-eclampsia. Am J Obst Gynecol, 185: 451-8.

Conde-Agudelo A, Althabe F, Belizan JM and Kafury-Goeta AC (1999): Cigarette smoking during pregnancy and risk of pre-eclampsia: A systematic review. Am J Obst Gynecol, 181: 1026-35.

Cnattingius S, Mills JL, Yuen J, Eriksson O and Salonen H (1997): The paradoxical effect of smoking in pre-eclamptic pregnancies: Smoking reduces the incidence but increases the rates of peri-natal mortality, abruptio placentae, and intrauterine growth restriction. Am J Obst Gynecol, 177: 156-61.

Cooper DW, Brennecke SP and Wilton AN (1993): Genetics of pre-eclampsia. Hypertension pregnancy, 12: 1-23.

Cross JC (1996): Trophoblast function in normal and preeclamptic pregnancy. Fetal Matern Med Rev, 8: 57-66.

Crowther C, Hiller J, Pridmore B, Bryce R, Duggan P, Hague WM and Robinson JS (1999): Calcium supplementation in nulliparous women for the prevention of pregnancy-induced hypertension, pre-eclampsia and preterm birth: An Australian randomized trial. Aust N Zealand J Obst Gynaecol, 39: 12-18.

Cunningham FG, Leveno KJ, Bloom SL, Hauth GC, Spong CU and Dwight JR (2010): Text book of Williams' obstetrics- Hypertensive disorder in pregnancy. 23th Ed, McGraw-Hill, New York.

Darby P and Wilson J (2002): Cyanide, smoking and tobacco amblyopia. Br J Ophthalmol, 51: 336-8.

Davey DA (1995): Hypertensive disorders of pregnancy. In: Dew Hurst's textbook of obstetrics and gynecology for postgraduate (Whitfield CR, ed), 5 Ed, 175-204, Black Well Scientific Publications.

Davies AM, Poznansky R, Weiskopf P, Prywes R, Sadovsky E and Czaczkes W (1976): Toxemia of pregnancy in Jerusalem. II. The role of diet. Isr J Med Sci, 12: 509-18.

Dekker GA, Robillard PY and Hulsey TC (1998): Immune maladaptation in the etiology of pre-eclampsia: A review of corroborative epidemiologic studies. Obst Gynecol Surv, 53: 377-82.

Duckitt K and Harrington D (2005): Risk factors for pre-eclampsia at antenatal booking: Systematic review of controlled studies. BMJ, 330: 565-7.

El-Houseinie M, Salama EI, Radwan M, Hemeida SA, Sammour MB and Faris R (1994): Development of a scoring system for the prediction of the unfavorable pregnancy outcome. Egypt J Comm Med, 12(1): 71-8.

Eras JL, Saftlas AF, Triche E, Gsu DC, Rich HA and Bracken MB (2002): Abortion and its effect on risk pre-eclampsia and transient hypertension. Epidemiology, 11:36-43.

Esplin MS, Fausett MB, Fraser A, Kerber R, Mineau G and Carrillo J (2001): Paternal and maternal components of the predisposition to pre-eclampsia. N Engl J Med, 344: 867-72.

Friedman SA, Schiff E, Lubarsky SL and Sibai BM (1999): Expectant management of severe pre-eclampsia remote from term. Clin Obst Gynecol, 42: 470-8.

Ferris TF (1990): Pregnancy complicated by hypertension and renal disease. Adv Intern Med, 35: 269-87.

Funai EF, Paltiel OB, Malaspina D, Friedlander Y, Deutsch SL and Harlap S (2005): Risk factors for pre-eclampsia in nulliparous and parous women: The Jerusalem perinatal study. Paediat Perinat Epidemiol, 19(1): 59-68.

Gadalla F, Abd El-Salam AF, Wassif SM, Khalifa SM, Foda MA, Ali AS and Abd El-Hamid ESH (1986): Differential magnitude of high risk pregnancy in rural and urban communities in Sharkia governorate. Egypt J Comm Med, 2(2): 157-65.

Gaym A (2000): Perinatal mortality audit at Jimma hospital, South Western Ethiopia, 1990-1999. Ethiop J Health Dev, 14(3): 335-43.

Goldenberg RL and Rouse DJ (1998): Prevention of premature birth. N Engl J Med, 339: 313-20.

Hauth JC and Cunningham FG (1999): Pre-eclampsia/eclampsia. In: Chesley's hypertensive disorders in pregnancy (Lindheimer M, Roberts J and Cunningham FG, eds.), 2nd Ed., 169-99. Stamford, CT: Appleton & Lange, New York.

Hays F and Smetter G (1986): Multiple gestation. Clinic Obst Gynecol, 29: 514-9.

Hernández-Díaz S, Van Marter LJ, Werler MM, Louik C and Mitchell AA (2007): Risk factors for persistent pulmonary hypertension of the newborn. Pediatrics, 120(2): e272-e82.

Herrera JA, Arevalo-Herrera M and Herrera S (1998): Prevention of pre-eclampsia by linoleic acid and calcium supplementation: A randomized controlled trial. Obst Gynecol, 91: 585-90.

Herrera JA, Chauduri G and López-Jaramillo P (2001): Is infection a major risk factor for preeclampsia? Medical Hypotheses, 57: 393-7.

Hill JA, Devoe LD and Bryans Jr CI (1986): Frequency of asymptomatic bacteriuria in preeclampsia. Obst Gynecol, 67: 529-32.

Howard J, Hankey BF, Greenberg RS, Austin DF, Correa P, Chen VW and Durako S (1992): A collaborative study of differences in the survival rates of black patients and white patients with cancer. Cancer, 69: 2349-60.

Hsu CD and Witter FR (1995): Urogenital infection in pre-eclampsia. Int J Gynaecol Obst, 49: 271-5.

Kolusari A, Kuroglu M, Yildizhan R, Adali E, Edirne T, Cebi A, Demir H and Yoruk I (2008): Catalase activity, serum trace element and heavy metal concentrations, and vitamin A, D and E levels in pre-eclampsia. J Internat Med Res, 36: 1335-41.

Kramer MS, Demissie K, Yang H, Platt RW, Sauve R and Liston R (2000): Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. The contribution of mild and moderate preterm birth to infant mortality. JAMA, 284: 843-9.

Kurki T, Hiilesmaa V, Raitaslo R, Mattia, H and Ylikorkala 0 (2000): Depression and anxiety in early pregnancy and risk for preeclampsia. Am J Obst Gynecol, 95(4): 487-90.

Lauro V, Pisani C and Zacche G (1997): Pre-eclampsia: Correlation between changes in symptomatology and changes in diet. Acta Biomed, 68(1): 95-8.

Li D-K and Wi S (2000): Changing paternity and the risk of pre-eclampsia/ eclampsia in the subsequent pregnancy. Am J Epidemiol, 151(1): 57-62.

Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E and Irgens LM (1998): Fetal and maternal contributions to risk of pre-eclampsia: Population based study. BMJ, 316: 1343-7.

Lin CC, Lindheimer MD, River P and Moawad AH (1982): Fetal outcome in hypertensive disorders of pregnancy. J Obst Gynecol, 1(14): 255-6.

Lindheimer MD, Roberts JM, Cunningham FG and Chesley L (1999): Introduction, history, controversies and definitions. In: Chesley's hypertensive disorders in pregnancy (Lindheimer M, Roberts J and Cunningham F, eds.), 2nd Ed., 3-41. Stamford, CT: Appleton & Lange, New York.

López-Jaramillo P, Casas JP and Serrano N (2001): Pre-eclampsia: From epidemiological observations to molecular mechanisms. Braz J Med Biol Res, 34 (10): 1227-35.

Lou SG, Amirabi A, Yazidian and Pashhapour (2008): Evaluation of serum calcium, magnesium, copper and Zinc levels in women with preeclampsia. IJMS, 33(4): 231-4.

MacGillivary A (1983): Pre-eclampsia: Hypertensive disease of pregnancy. WB, Saunders Company.

Mahaba HM, El-Taweel RM and Hafez AS (2001a): Dietary pattern and nutritional status in preeclampsia. Egypt J Comm Med, 19(3): 1-8.

Mahaba HM, Ismail NA, El-Damaty SI and Kamel HA (2001b): Pre-eclampsia: Epidemiology and outcome 995 cases. J Egypt Public Health Assoc, LXXVI (5&6): 357-68.

Marshall W and Carpenter MD (2007): Gestational diabetes, pregnancy hypertension, and late vascular disease. Diabetes Care, 30: 246-50.

Meis P, Goldenberg R and Mercer B (1998): The preterm prediction study: Risk factors for indicated preterm birth. Am J Obst Gynecol, 179: 562-7.

Midthjell K, Krüger Ø and Holmen J (1999): Rapid changes in the prevalence of obesity and known diabetes in an adult Norwegian population: The Nord-Trøndelag Health Surveys: 1984-1986 and 1995-1997. Diabetes Care, 22: 1813-20.

Mittendorf R, Lain KY, Williams MA and Walker CK (1996): Preeclampsia: A nested case-control study for risk factors and their interactions. J Reprod Med, 41: 491-6.

Mohammed AS (2009): Epidemiological study of hypertension in Dar El-Salsm Hospital, Sohag Governorate. Master Thesis in Community Medicine, Faculty of Medicine, Al-Azhr University.

Morris CD, Jacobson SL, Anand R, Ewell MG, Hauth JC, Curet LB, Catalano PM, Sibai BM and Levine RJ (2001): Nutrient intake and hypertensive disorders of pregnancy: Evidence from a large prospective cohort. Am J Obst Gynecol, 184: 643-51.

Murray MT and Pizzorno JE (2006): Stress management. In: Textbook of natural medicine, (Pizzorno Jr JE and Murray MT, eds.), 1: 701-8.

Nilsson E, Salonen Ros H, Cnattingius S and Lichtenstein P (2004): The importance of genetic and environmental effects for pre-eclampsia and gestational hypertension: A family study. BJOG, 111: 200-6.

Nosseir SA; Mortada MM; Nofal LM; Dabbous NI and Ayoub AI (1990): Screening for high risk pregnancy among mothers attending MCH centers in Alexandria. J Egypt Public Health Assoc, LXV (5&6): 463-83.

Odegard RA, Vatten LJ, Nilsen ST, Salvesen KA and Austgulen R (2000): Risk factors and clinical manifestations of pre-eclampsia. BJOG, 107: 1410-6.

Ostlund I, Haglund B and Hanson U (2004): Gestational diabetes and preeclampsia. Eur J Obst Gynecol Reprod Biol, 113: 12-6.

Pipkin FB (2001): Risk factors for preeclampsia. N Engl J Med, 344: 925-6.

Raijmakers MTM, Dechend R and Poston L (2004): Oxidative stress and pre-eclampsia: Rationale for antioxidant clinical trials. Hypertension, 44: 374-80.

Report the Task Force ACOG/AAP (2003): Neonatal encephalopathy and cerebral palsy: Defining the pathogenesis and pathophysiology. American College of Obstetricians & Gynecologists and American Academy of Pediatrics, Washington, DC.

Roberts JM (1998): Pregnancy related hypertension. In: Maternal fetal medicine, (Creasy RK and Resnik R, eds.), 4th Ed, WB Saunders, Philadelphia.

Roberts JM, Balk JL, Bodnar LM, Belizán JM, Bergel E and Martinez A (2003a): Nutrition as a preventive strategy against adverse pregnancy outcomes- Nutrient involvement in pre-eclampsia. J Nutr, 133: 1684S-92S.

Roberts JM and Cooper DW (2001): Pathogenesis and genetics of pre-eclampsia. Lancet, 357: 53-6.
Roberts JM and Gammill H (2006): Insulin resistance in preeclampsia. Hypertension, 47: 341-2.
Roberts JM and Hubel CA (1999): Is oxidative stress the link in the two-stage model of pre-eclampsia? Lancet, 354: 788-9.
Roberts JM and Lain KY (2002): Recent insights into the pathogenesis of pre-eclampsia. Placenta, 23: 359-72.
Roberts JM, Pearson G, Cutler J and Lindheimer M (2003b): Summary of the NHLBI Working Group on Research on Hypertension during Pregnancy. Hypertension, 41: 437-45.
Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA and McLaughlin MK (1990): Pre-eclampsia: An endothelial cell disorder. Am J Obst Gynecol, 163: 1365-7.
Ros HS, Cnattingius S and Lipworth L (1998): Comparison of risk factors for pre-eclampsia and gestational hypertension in a population-based cohort study. Am J Epidemiol, 147: 1062-70.
Rosalia M, Terasa P, Keyla C, Fulgencia P and Reinaldo M (1998): Preeclampsia lipid peroxidation and calcium triphospatase acclivity red blood cell ghosts. Am J Obst Gynecol, 178: 402-8.
Sacks GP, Studena K, Sargent IL and Redman CWG (1998): Normal pregnancy and pre-eclampsia both produce inflammatory changes in peripheral blood leukocytes akin those of sepsis. Am J Obst Gynecol, 179: 80-6.
Scioscia M, Gumaa K and Rademacher TW (2009): The link between insulin resistance and preeclampsia: new perspectives. J Reprod Immunol, 80(1-2): C02.
Sibai BM (2003): Diagnosis and management of gestational hypertension and preeclampsia. Obst Gynecol, 102: 181-92.
Sibai BM, Ewell M, Levine RJ, Klebanoff MA, Esterlitz J, Catalano PM, Goldenberg RL AND Joffe G (1997): Risk factors associated with pre-eclampsia in healthy nulliparous women. Transactions of the Seventeenth Annual Meeting of the Society of Perinatal Obstetricians. Am J Obst Gynecol, 177(5): 1003-10.
Sibai BM, Hauth J and Caritis S (2000): Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Am J Obst Gynecol, 182: 938-42.
Sibai BM, Mabie BC, .Harvey CJ and Gonawlez AR (1987): Pulmonary edema in sever preeclampsia-eclampsia: Analysis of thirty seven consecutive cases. Am J Obst Gynecol, 156(51): 1174-9.
Skjaerven R, Vatten LJ, Wilcox AJ, Rønning T, Irgens LM and Lie RT (2005): Recurrence of pre-eclampsia across generations: Exploring fetal and maternal genetic components in a population based cohort. BMJ, 331(7521): 877-85.
Skjaerven R, Wilcox AJ and Lie RT (2002): The interval between pregnancies and the risk of pre-eclampsia. N Engl J Med, 346: 33-8.
Solmon CG and Seely EW (2004): Preeclampsia: Searching for the cause. N Engl J Med, 350: 641-2.
Surratt N (1993): Severe pre-eclampsia: Implications for critical-care obstetric nursing. J Obst Gynecol Neonatal Nurs, 22: 500-7.
Taylor RN and Roberts JM (1999): Endothelial cell dysfunction. In: Chesley's hypertensive disorders in pregnancy (Lindheimer M, Roberts J and Cunningham FG, eds.), 2nd Ed., 395-429. Stamford, CT: Appleton & Lange, New York.
Tobe SW, Kiss A and Szalai JP (2005): Impact of job and marital strain on ambulatory blood pressure: Results from the Double Exposure study. Am J Hyperten, 23: 717-8.
Vambergue A, Nuttens MC, Goeusse P, Biausque S, Lepeut M and Fontaine P (2002): Pregnancy induced hypertension in women with gestational carbohydrate intolerance: The digest study. Eur J Obst Gynecol Reprod Biol, 102: 31-5.
Vatten LJ, Skjaerven R (2004): Is pre-eclampsia more than one disease? BJOG, 11: 298-302.
Wang J (2003): The length of sexual relation is related to the incidence of pre-eclampsia? BJOG, 10: 195-9.
Wang J, Knottnerus A, Schuit G, Norman R, Chan A and Dekker G (2002): Surgically obtained sperm, and the risk of gestational hypertension and pre-eclampsia. Lancet, 359: 674-9.
White P (1965): pregnancy and diabetes: Medical aspects. Med Clin North Am, 49: 1015-26.
WHO (1987): The hypertensive disorders of pregnancy. WHO Technical Report Series, No 758, Geneva.
WHO (2000): Obesity: Preventing and managing the global epidemic. WHO Technical Report Series, Geneva.
Wolf M, Sandler L, Munoz K, Hsu K, Ecker JL and Thadhani R (2002): First trimester insulin resistance and subsequent preeclampsia: A prospective study. Clin Endocrinol Metab, 87: 1563-8.
Xiong X, Demianczuk NN, Buekens P and Saunders LD (2000): Association of pre-eclampsia with high birth weight for gestational age. Am J Obst Gynecol, 183: 148-55.
Yeo S and Davidge ST (2001): Possible beneficial effect of exercise, by reducing oxidative stress, on the incidence of preeclampsia. J Women's Health Gend Based Med, 10(10): 983-9.
Zhang C, Williams MA, King IB, Dashow EE, Sorensen TK, Frederick IO, Thompson ML and Luthy DA (2002): Vitamin C and the risk of pre-eclampsia: Results from dietary questionnaire and plasma assay. Epidemiology, 13: 409-16.
Ziaei S, Ranjkesh F and Faghihzadeh S (2008): Evaluation of 24-hour copper in preeclamptic vs. normotensive pregnant and non-pregnant women. Intrnat J Fert Ster, 2(1): 9-12.

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