Biochemical effect of pre eclampsia on endothelin-1 , interleukins and high sensitivity CRP

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A B S T R A C T

Preeclampsia is multisystem disorder, of unknown etiology. It is characterized by vasospasm, multiple organ hypoperfusion and endothelial cell damage. Many of its signs and symptoms can be explained by an imbalance in vasomotor tone-regulating factors, including endothelin-1(ET-1) and mediators of an inflammatory response, including C-reactive protein (CRP). Determination of high sensitivity CRP (hs-CRP)has been suggested to be more sensitive than conventional measurement of CRP and it provided better sensitivity in establishing an inflammation. The aim of this work is to the association of inflammatory marker high sensitivity C-reactive protein (hs-CRP), Endothelins-1, interleukin-1 and interleukin-4 with preeclampsia in pregnant women. This study was carried out on 80 female, who were divided into four equal groups of 20 woman each. The first group represent control group, included non-pregnant healthy female subjects. The second group was the pregnant control group; the third group was the patient group, included pregnant women with mild pre-eclampsia. In addition, the fourth group represented by pregnant women with sever pre-eclampsia for plasma endothelin-1, Serum hs-CRP, interleukin-1 and interleukin-4 were measured in all groups. At the gestational period of 20-24 weeks, plasma endothelin-1, and serum hs-CRP were significantly elevated in preeclamptic patients compared to pregnant and non-pregnant woman ($p<0.05$).

Keywords: Pre-eclampsia, plasma endothelin-1, high sensitivity CRP, interleukin-1, interleukin-4.

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1. INTRODUCTION

Preeclampsia (PE) is the most common encountered complication of pregnancy and leads to maternal and neonatal mortality worldwide (Al-Jameil et al., 2014). Preeclampsia is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks' gestation and could be continue as late as 4-6 weeks postpartum. It is clinically defined by hypertension and proteinuria, with or without pathologic edema. The incidence of preeclampsia in the United States is estimated to range from 2% to 6% in healthy, nulliparous women (Sibai., 2003 and Vatten and Skjaerven , 2004). In Egypt, the prevalence of PE is 10.7% in a community based study (Gadalla et al., 1986). Among all cases of the preeclampsia, 10% occur in pregnancies of less than 34 weeks' gestation. The global incidence of preeclampsia has been estimated at 5-14% of all pregnancies. In developing nations, the incidence of the disease is reported to be 4-18% (Khedun et al.,1997 and Villar et al., 2001),with hypertensive disorders being the second most common obstetric cause of stillbirths and early neonatal deaths in these countries (Ngoc et al.,2006). These polypeptides are potent vasoconstrictors, and endotheline-1 is the only produced by human endothelium (Mastrogiannis and co-workers., 1991). The vascular endothelium itself is responsible for a number of homeostatic functions

within normal blood vessels, including the hemostatic function of maintaining vascular tone. The endothelium achieves this in part through the production and release of a variety of relaxing and constricting factors, including the vasoactive peptide endothelin (ET).1 The normal endothelium also has antithrombotic properties that can turn prothrombotic if the endothelium is perturbed or injured (Braunwald et al, 2001). C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via the C1Q complex.(Thompson et al., 1999). CRP is synthesized by the liver (Pepys and Hirschfield., 2003) in response to factors released by fat cells (adipocytes) (Lau et al.,2005). It is a member of the pentraxin family of proteins (Pepys and Hirschfield., 2003) . therefore was the first pattern recognition receptor (PRR) to be identified (Mantovani et al.,2008). It was initially thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illnesses including cancer (Pepys and Hirschfield, 2003). However, discovery of hepatic synthesis demonstrated that it is a native protein (Peter et al., 2009). CRP level was found to be raised in healthy pregnant compared with non-Pregnant women. However, factors such as age, labour, infections and medical diseases are associated with raised concentrations of CRP (Hwang et al., 2007). During the pregnancy, there is a shift in immune cells response for favorable implantation, thus inducing maternal tolerance and suppression (Wegmann., 1993) . In women with PE some of the cytokines released by these cells have been found to be elevated, which could be markers for progression of this syndrome (Mohajertehran et al., 2012). Interleukin- 4 is the main cytokine of T helper 2 lymphocytes, which has a key role in regulation of humoral immune responses (Rezaei et al., 2010). The production of this anti-inflammatory cytokine should increase during pregnancy. Thus, the function of immune system alters during PE. Interleukin-4 (IL4) gene ismapped within the cytokine gene cluster on chromosome 5q31.1 (Jha et al., 2012). IL-4 was first described by William Paul and co-workers in 1982, upon discovering that supernatants From phoibol-myristate acetate (PMA)-stimulated IL-4 thymoma cells were of supporting the growth of anti-Ig- stimulated B cells. The factor in these supernatant was identified as helper for B cell proliferation, induced IgM. B cells to enter the S phase of cell cycle, distinct from IL-2 and was initially called B-Cell Growth Factor (Howard et al., 1982). In addition, (Omu et al., 1995) stated that IL-4 was observed as a co-stimulator of B-cell DNA synthesis in response to antiimmunoglobulin M antibodies. Further more PE is an excessive systemic inflammation response with dysfunction of endothelial (Rusterholz et al 2007). The serum levels of several cytokines, such as IL-1, TNF-α, IL-6, IL-8, are increased in PE patients (Amash et al., 2012, Szarka et al., 2010). IL-1 is a critical mediator of the inflammatory response and important factor that stimulates the structural and functional alterations in endothelial cells (Rusterholz et al., 2007). IL1 & TNF-α are structurally unrelated cytokines, and bind to different cellular receptors, yet their spectrum of biological effects, so resemble one another, dial the two cytokines are almost interchangeable (Operheim et al., 1994). The relation of IL1 to the development of pre-eclampsia is not yet clear. Because of the altered prostaglandin synthesis plays an important role in pre-eclampsia, IL-IB has been investigated in this context. However, its concentration in maternal serum or amniotic fluid were unchanged in pre-eclamptic cases (Kupfermine et al., 1995 and Raynor., 1996). However, the administration of recombinant human IL-IB (rh-lLB), for treatment of patients with bone marrow failure; was complicated by

hypertension in 89% of cases (Nemunaitis et al., 1994), while treatment of rats induce pulmonary hypertension, also treatment by IL-I receptor antagonist (IL-Ira) ; prevent the development of this condition (Voelket et al., 1994).

2. MATERIAL AND METHODS

Serum and plasma samples were obtained from 80 female their ages ranged from 20 to 40 years They were admitted to Benha university Hospital. and Ain Shams Hospital for Gynecology and Obstetrics,who were classified into 4 equal groups. The first group represent control group, included 20 non- pregnant healthy female subjects. The second group was the pregnant control group, included 20 pregnant female subjects. The third group was the patient group, included 20 pregnant women with pre-eclampsia . And The fourth group represented by 20 pregnant women with sever pre-eclampsia. All subjects were asked to join the study and were informed about the aim of the work, The subjects were recruited from normotensive , pregnant >20weeks, non-smokers.

Exclusion Criteria: History of medical disorder e.g. renal, hepatic, immunological or diabetic disease. Present or past history of hypertension (>140/90). Prenatal or postnatal diagnosis of a chromosomal or structural abnormality. Lost subjects at follow visits.

All subjects were followed up according to ANC protocol. All subjects were subjected for:

2-1- Full History Taking Including:

Personal history, Present history, Past medical and surgical history and Family history especially of hypertension, preeclampsia or eclampsia.

2-2- Complete Physical Examination:

Included recording the vital sings, head neck examination, examination for cardiovascular diseases, liver and renal diseases, anemia, malnutrition or other medical or surgical illness. The patient was then weighed.

2-3- Preparation of Blood samples and Biochemical analysis:

Blood samples were collected in dry, clean and screw capped tubes. Serum incubated for 1/2 hr at room temperature to allow clotting for serum separation, clear sera were separated by centrifugation at 3500 r.p.m. for 15 minutes, and then collected in Eppendorf's tubes using automatic micropipettes. Then were kept in a deep freeze at -20°C until used for subsequent biochemical analysis . Serum High Sensitive C-Reactive protein was assessed by (ELISA) according to (Abdel-Rahman., 2007), serum IL-4 according to (Bancheau., 1990) and serum IL——1. Also blood was collected using EDTA as an anticoagulant. then was Centrifuged for 15 minutes at 1000 x g within 30 minutes of collection. Extracted plasma was assessed immediately for determination of Endothelin-1 according to (Burg et al., 2011).

3. RESULTS

Biochemical effect of pre eclampsia on endothelin-1, interleukins and high sensitivity CRP in preeclamptic patients compared to normal pregnant and non-pregnant woman were statistically analyzed and represented in the table.

3.1. Plasma (Endothelin1)

There was significant increase in mild and severe pre eclampsia compared to controls *(P> 0.05)* and there was significant increase in severe pre eclampsia compared to mild pre eclampsia and to controls *(P> 0.05).*

3.2. Serum Sensitive C-Reactive protein

There was significant increase in mild and severe pre eclampsia compared to controls *(P> 0.05)* and there was significant increase in severe pre eclampsia compared to mild pre eclampsia and to controls *(P> 0.05).*

3.3. Serum interleukin-1

There was significant increase in mild and severe pre eclampsia compared to controls *(P> 0.05)* and there was significant increase in severe pre eclampsia compared to mild pre eclampsia and to controls *(P> 0.05).*

There was significant increase in mild and severe pre eclampsia compared to controls *(P> 0.05)* and there was significant increase in severe pre eclampsia compared to mild pre eclampsia and to controls *(P> 0.05).*

3.4. Serum interleukin-4

Table (1): Mean Value of plasma endothelin-1 , Serum hs-CRP , interleukin-1 and interleukin-4 level of Pre-eclampsia cases compared with control pregnant and non pregnant healthy females.

Parameter tes	Groups			
	Control (-ve) Non pregnant group	Control (+ve) pregnant group	Mild Pre-eclampsia group	Sever Pre-eclampsia group
Endothelin1 (pg/ml)	0.32±0.03[a]	0.65±0.03[b]	1.26±0.04[c]	2.49±0.12[d]
hs-CRP (mg/dl)	0.63±0.05a	1.25±0.1a	10.12±0.24b	22.19±0.75c
IL1 (pg/ml)	203.05±24.38[a]	273.00±22.76[a]	386.25±40.62[b]	584.65±46.88[c]
II4 (pg/ml)	0.32±0.02[a]	2.33±0.25[b]	8.13±0.61[c]	15.03±0.79[d]

SE: standard error. a, b & c: The difference in the superscript letters with the same row indicate significant difference *(P< 0.05)*

4. DISCUSSION

Pre-eclampsia is a pregnancy-specific syndrome of unknown etiology, manifested by hypertension, proteinuria, edema and activation of coagulation cascade, which resolve rapidly following delivery. It is a late manifestation of a multifactorial, multisystem disease that is initiated very early in pregnancy *(Cunningham et al., 2001).* Severe PE is associated with an increased risk of many adverse maternal and fetal outcomes. The ultimate consequence of PE is varying degrees of ischemic end-organ damage and this process is explained by diffuse maternal endothelial dysfunction. There is evidence suggesting that normal pregnancy itself stimulates maternal inflammatory response, *(Hwang et al., 2007)* and that in PE, there is an enhanced systemic maternal inflammatory process to pregnancy *(Redman et al., 1999)*. Our result's revealed that the mean value of Endothelin-1 levels were significantly higher in mild and sever pre eclampsia compared to pregnant and non pregnant woman (*P> 0.05*). As, Endothelin-1 may play a part in pathophysiologic make-up of several conditions that are associated with vasoconstriction. in preeclampsia the increased plasma levels of endothelin-1 are due to an enhanced activity of the endothelial system which includes an increased conversion of big endothelin-1 to endothelin-1 *(*Wagner, et al.,*2006)*. It has been showed that plasma levels of endothelin-1 decreased in second trimester during normal pregnancy (Allaire et al., 2000). Because of endothelin-1 powerful vasoconstrictive properties, this observation may provide an explanation for the falling of blood pressure during mid-pregnancy and contribute to normal cardiovascular adaptation. The mean valus of hs-CRP it was significantly higher in

mild PE compared to normotensives (*P> 0.05*) Further more in severe pre eclampsia compared to mild pre eclampsia (*P> 0.05*) , Also in severe pre eclampsia compared to normotensives. High sensitive CRP is a marker of systemic low-grade inflammation, an acute phase reactant produced in the liver as a response to stress, tissue injury and is the most sensitive glycoprotein marker of overall inflammatory activity in the body *(Ertas et al., 2010).(Ertas et al., 2010)* pointed out that since hs-CRP is easily monitored in laboratories, and is considerally less expensive to assay in comparison to other inflammatory and endothelial damage cytokines, hs-CRP is useful in the evaluation of patients with mild and severe PE. Moreover the mean values of interleukin-1 and interleukin-4 were significantly higher in mild PE compared to normotensives (*P> 0.05*) Further more in severe pre eclampsia compared to mild pre eclampsia (*P> 0.05*) , Also in severe pre eclampsia compared to normotensives. The normal pregnancy is suggested to be a condition of controlled mild maternal systematic inflammation. And exaggerated inflammation is proposed to play an important role in the development of PE (Amash et al., 2012) and (Sazarka, et al., 2010)There is Th1/Th2 imbalance in PE patients, and Th1 immunity is predominant in the immune and inflammatory response (Darmochwal- Kolarz et al., 2002). Among the Th1-type pro-inflammatory cytokines, IL-1 initiates and perpetuates inflammatory response. The levels of IL-1 was higher in PE patients (Amash et al., 2012). IL-1 can stimulate expression and activity of matrix metalloproteinase (MMP) 9 and MMP2, thus regulate trophoblast differentiation along the invasive pathway, which may affect the process of placentation (Meisser et al., 1999). Moreover, IL-1 can alter the structure and function of endothelial cells. IL-1 produced by placenta altered the proliferation of umbilical vein endothelial cell (Rusterholz et al., 2005), whose serum levels were increased in PE patients. Therefore, IL-1 is a potential mediator of endothelial dysfunction and may involve in the development of PE. Furthermore, the associations between polymorphisms of IL-1 and the risk of PE have also been investigated. However, because of mutations, genetic recombination, human mobility and natural selection, the frequencies of genotypes and alleles are different in the population from different race or region, therefore the results of these studies are controversial due to IL-1β showed no associations with the risk of PE (Mohajertehran et al., 2012 , Valencia (Villalvazo et al., 2012) .

5. CONCLUSION

Thus, it could be concluded that the level of plasma Endothlin-1, h.s. CRP , IL-1 and IL-4 were associated with severity of pre eclampsia in pregnant women .thus it could be recommended for prediction of development of pre eclampsia in pregnant woman .

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الدراسه الكيميائية الحيوية لتأثير تسمم الحمل على إندوثيلين (1) ومستوى بروتين سي النشط

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قسم الكيمياء الحيوية-كلية الطب البيطري بمشتهر-جامعة بنها

مرض تسمم الحمل من الأمراض الخطيرة التي تصيب السيدات الحوامل، والذي يتم تشخيصه بارتفاع ضغط الدم وزيادة نسبة الزلال في البول وقد وجد أن هذا المرض يصيب حوالي 4 الى 18% من السيدات الحوامل.ويعد هذا المرض ثانى أكبر سبب فى وفيات الأمهات فى العالم وهناك عدة نظريات حاولت تفسير هذا المرض الخطير ولكن مايزال السبب الحقيقي لتسمم الحمل غير مؤكد، ومن المحتمل أن يكون زرع التروفوبلاست في الغشاء المبطن للرحم ضعيفا، مما يؤدي الى ضعف الدورة الدموية بالمشيمة، وهو أحد العوامل المؤدية الى مرض تسمم الحمل. ومنع هذا المرض يتطلب ليس فقط معرفة ميكانيكيته الباثولوجية والفسيولوجية، ولكن أيضاً تيسير الوسائل التي تساعد على اكتشافه اكتشافاً مبكراً. كما أن إصابة الخلايا المبطنة لجدر الأوعية الدموية لها ميكانيكية باثولوجية أساسية في مرض تسمم الحمل، ينتج عن ذلك تأليف ضعيف للمواد الموسعة للأوعية الدموية، وزيادة محتملة في إنتاج المواد القابضة للأوعية الدموية. استهدفت هذه الدراسة قياس نسبة الأيندوثيلين -1 ببلازما الدم وايضا بروتين ج النشط العالي الحساسية في السيدات التي تعاني من تسمم حمل طفيف وشديد ومقارنتها بسيدات حوامل طبيعيه وأخرى ليست حاملا بهدف التنبؤ بهذه المتلازمه من خلال ربط مستوى القياسات التي تمت بمراحل المرض. اشتملت هذه الدراسة على80 مصرية حاملا فى جنين واحد فى الثلاث شهور الأخيرة من الحمل ويتراوح أعمارهن بين 20 إلى 40 سنة وقد تم اختيارهن من قسم النساء والتوليد بمستشفيات جامعة بنها وعين شمس وقد تم تقسيم الحوامل إلى ثلاثة مجموعات متساوية: -المجموعة الاولى: تشتمل على 20 سيده غير حامل وضغط الدم طبيعي. المجموعة الثانية (المجموعة الضابطة): تشتمل على 20 حامل حملا" طبيعيا" وضغط الدم طبيعي.
المجموعة الثالثة (مجموعة ما قبل الارتجاج الخفيف): وتشتمل على 20 سيدة يعانين من قبل ارجاج خفيف' أي وجود ارتفاع فى ضغط الدم قيمتة 90/140 م.م زئبقى أو أكثر مع وجود زلال +1 أو أكثر بالبول. المجموعة الرابعه (مجموعة ما قبل الأرجاج الشديد): وتشتمل على 20 سيدة يعانين من ما قبل ارجاج شديد، اى وجود ارتفاع فى ضغط الدم قيمته 90/160 م.م زئبقى أو أكثر أو وجود +2 أو أكثر بالبول أو وجود زلال أعراض شدة المرض مثل الصداع، مشاكل فى الابصار، ألم بأعلى البطن أو قلة كمية البول. وقد تم أخذ تاريخا مرضيا" كاملا" وإجراء فحصا" إكلينيكيا كاملا" اتبعه عمل فحوصات لصورة الدم ووظائف الكلى والكبد. وقد سجلت الدراسة ارتفاع مستوى اندوثيلين-1 وأيضا مستوى البروتين ج النشط ومستوى الانتر لوكين -1 والانتر لوكين -4 في دم السيدات المصابات بتسمم الحمل عنه في مصل السيدات الحوامل حملا طبيعيا ، و كذلك في دم السيدات الطبيعيات غير الحوامل.

(مجلة بنها للعلوم الطبية البيطرية: عدد 27(2):209-216, ديسمبر 2014)