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Relationship between gender of fetus and the EEG changes and the relation of these changes with some inflammatory biomarkers in preeclamptic pregnant females

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Abstract:

Background: The electroencephalograph records spontaneous electrical activity generated in the cerebral cortex. This activity reflects the electrical currents that flow in the extracellular spaces of the brain that are the summated effects of innumerable excitatory and inhibitory synaptic potentials upon cortical neurons. Preeclampsia is a disease of pregnancy characterized by a blood pressure of 140/90 mmHg or more on two separate occasions after 20^{th} week of pregnancy in a previously normotensive woman. This is accompanied by significant proteinuria (>300 mg in 24 hours) (Philip, 2006).

Subjects and methods: The study included 97 pregnant patients with a confirmed diagnosis of preeclampsia, also 72 females with normal pregnancy have been included as a control group. Their ages and gestational ages were consistent with that of the patients', EEG test and some serological tests including ICAM-1, RCRP and IL-6 was done for the participants.

Results: There was a high percentage of EEG changes in the preeclamptic women whom fetus are males. There was a significant differences in the values of the interleukin-6 (IL-6) between preeclamptic women with male fetus and those with female one.

Electroencephalography (EEG):

The electroencephalograph records spontaneous electrical activity generated in the cerebral cortex. This activity reflects the electrical currents that flow in the extracellular spaces of the brain that are the summated effects of innumerable excitatory and inhibitory synaptic potentials upon cortical neurons (Ropper and Samuels, 2009). An EEG signal is a measurement of currents that flow during synaptic excitations of the dendrites of many pyramidal neurons in the cerebral cortex. When brain cells (neurons) are activated, the synaptic currents are produced within the dendrites. This current generates a magnetic field measurable by electromyogram (EMG) machines and a secondary electrical field over the scalp measurable by EEG systems. Differences of electrical potentials are caused by summed postsynaptic graded potentials from pyramidal cells that create electrical dipoles between the soma (body of a neuron) and apical dendrites, which branch from neurons. The current in the brain is generated mostly by pumping the positive ions of sodium (Na^+), potassium (K^+) and calcium (Ca^{++}) and the negative ion of chloride (Cl^-) through the neuron membranes which governed by the membrane potential (Attwood and MacKay 1989).

Electrical signals are created when electrical charges move within the central nervous system. Neural function is normally maintained by ionic gradients established by neuronal membranes. Sufficient duration and length of small amounts (in microvolts) of electrical currents of cerebral activity are required to be amplified and displayed for interpretation. A resting (diffusion)

membrane potential normally exists through the efflux of positive-charged (potassium) ions maintaining an electrochemical equilibrium of –75 mV. With depolarization, an influx of positive-charged (sodium) ions that exceeds the normal electrochemical resting state occurs. Channel opening within the lipid bilayer is via a voltage-dependent mechanism, and closure is time dependent. Conduction to adjacent portions of the nerve cell membranes results in an action potential when the depolarization threshold is exceeded. However, it is the synaptic potentials that are the most important source of the extracellular current flow that produces potentials in the EEG. Excitatory postsynaptic potentials (EPPs) flow inwardly (extracellular to intracellular) to other parts of the cell (sinks) via sodium or calcium ions. Inhibitory post-synaptic potentials (IPPs) flow outwardly (intracellular to extracellular) in the opposite direction (source), and involve chloride or potassium ions (Tatum, 2007).

Layers of cortical neurons are the main source of the EEG. Pyramidal cells are the major contributor of the synaptic potentials that make up EEG. These neurons are arranged in a perpendicular orientation to the cortical surface from layers III, IV, and VI (Kim *et al.*, 2005). Volumes large enough to allow measurement at the surface of the scalp require areas that are >6 cm2 , although probably >10 cm2 are required for most IEDs to appear on the scalp EEG because of the attenuating properties incurred by the skull. All generators have both a positive and negative pole that function as a dipole. The EEG displays the continuous and changing voltage fields varying with different locations on the scalp (Tatum, 2007).

Activity recorded by EEG:

Many brain disorders are diagnosed by visual inspection of EEG signals. The clinical experts in the field are familiar with manifestation of brain rhythms in the EEG signals. In healthy adults, the amplitudes and frequencies of such signals change from one state of a human to another, such as wakefulness and sleep. The characteristics of the waves also change with age. There are five major brain waves distinguished by their different frequency ranges. These frequency bands from low to high frequencies respectively are called alpha (α), theta (θ), beta (β), delta (δ), and gamma (γ).

Preeclampsia:

Preeclampsia is a disease of pregnancy characterized by a blood pressure of 140/90 mmHg or more on two separate occasions after 20th week of pregnancy in a previously normotensive woman. This is accompanied by significant proteinuria (>300 mg in 24 hours) (Baker, 2006).

The prevalence of preeclampsia is 5% to 7% of primigravida women where the disease is primary (in women with normal blood pressure before pregnancy and returns to normal after delivery). In women with chronic hypertension and especially those with renal disease, the incidence is much higher as preeclampsia is being superimposed on the existing hypertension (Mounira and Baha, 2003).

Although underlying pathophysiology is not so definite, it is mostly attributed to a generalized arteriolar constriction (vasospasm) and intravascular depletion secondary to a generalized transudative edema. This can produce symptoms related to ischemia, necrosis, and hemorrhage of organs. Thus, one of the fundamental aspects of the disease is vascular damage and an imbalance

in the relative concentrations of prostacyclin and thromboxane (Philip, 2006). It is theorized that this is primarily related to circulating antibodies or antigen-ntibody complexes that damage the lining of vessel walls leading to exposure of the underlying collagen structure. The hyperdynamic state of pregnancy has also been proposed to cause this underlying vascular injury rather than an immunogenic phenomenon (Tamara and Aaron, 2005).

Subjects and Methods:

The study included 97 pregnant patients with a confirmed diagnosis of preeclampsia with a gestational age ranging between 20-38 weeks. Their ages was ranging between 25-38 years.

Furthermore, 72 females with normal pregnancy have been included as a control group. Their ages and gestational ages were consistent with that of the patients'.

The participants belong to both patient and control groups were selected randomly and examined in gynecology and obstetrics hospital, in Karbala city, between January 2012 and June 2013. All of them were exposed to the same procedures and investigations that include history taking, physical examination, measuring her blood pressure, pulse rate and body temperature, electroencephalography (EEG) and serological tests including : Intracellular Adhesion Molecule 1 (ICAM-1), interleukin-6 (IL6) and C-reactive protein (CRP) in parallel.

Participants with any previous neurological abnormalities, a history of smoking or alcoholism and/or a febrile illness at the time of the visit. Furthermore, any participant with a suspicion of epilepsy through the medical history was excluded from the study.

Electroencephalography examination:

Computerized EEG system 2011 device was used for this purpose which consists from head box and interface to the PC unit is obtained via Shanghai NCC, 20 channels system.

Also, a network of cub electrode cables, neoprene elastic cap with rubber chin strap and adhesive conductive paste (Ten20) are also used as additional accessories.

The bipolar and referential montage according to the international 10-20 recording system was used.

The participant was reassured that the test is painless and allowed to relaxed and lie comfortable at 45° on the couch, the room temperature was kept around 25 C°.

The elastic cap was placed properly over the head to fix the electrodes that were placed on the scalp after being cleaned with rectified spirit then use the ten20 conductive paste to reduce resistance. Twenty one cub electrodes were used and allocated according to the international 10-20 system. After operating the devise, patient name, birth date were added by creating a new file for each patient. The electrode impedance was kept below 20 kΩ. The recording period continued for at least 30 minutes during which the patient was asked to relax and open her eyes for few minutes then close her eyes for few minutes. Furthermore, some provocative tests have been done that included hyperventilation (3 minutes of deep rapid breath 17 cycles per minute) with photic and sound stimulation.

The recorded EEG waves were averaged, amplified and filtered with band frequencies of 0.5-30 Hz, sweep speed 15-30 second/page and sensitivity of 30-50 uv/cm. The EEG trace is saved for reanalysis.

Analysis of EEG record:

The epileptic discharges (EDs) were defined as spike or sharp wave discharges that clearly stood out from the background rhythms, with or without an after going slow wave (Selvitelli *et. al*., 2011), and it was divided into four groups (International Federation of Societies for Clinical Neurophysiology, 1999):

1. Sharp wave: Transient, clearly distinguishable from background activity, with pointed peak at conventional paper speeds and a duration of 70-200 milliseconds (ms).
2. Spike: same as sharp wave, but with duration of 20 to less than 70 ms.
3. Spike and slow-wave complex: pattern consisting of a spike followed by a slow wave (classically the slow wave being of higher amplitude and wide duration than the spike).
4. Multiple spike and slow-wave complex: same as spike and slow-wave complex, but with 2 or more spikes associated with one or more slow waves.

Laboratory Investigation :

By doing ELISA technique to detect the values of ICAM-1, CRP and IL-6.

Results:

1- There was a high percentage of preeclampsia in women whom fetus are males.
2- There is no significant differences in the percentage of EEG changes between preeclamptic females with male fetus and those with female ones.
3- There was a significant differences in the values of the interleukin-6 (IL-6) between preeclamptic women with male fetus and those with female one.
4- There was no significant changes in the values of intracellular adhesion molecules (ICAM-1) and C-reactive protein (CRP) between preeclamptic women with male fetus and those with female one.

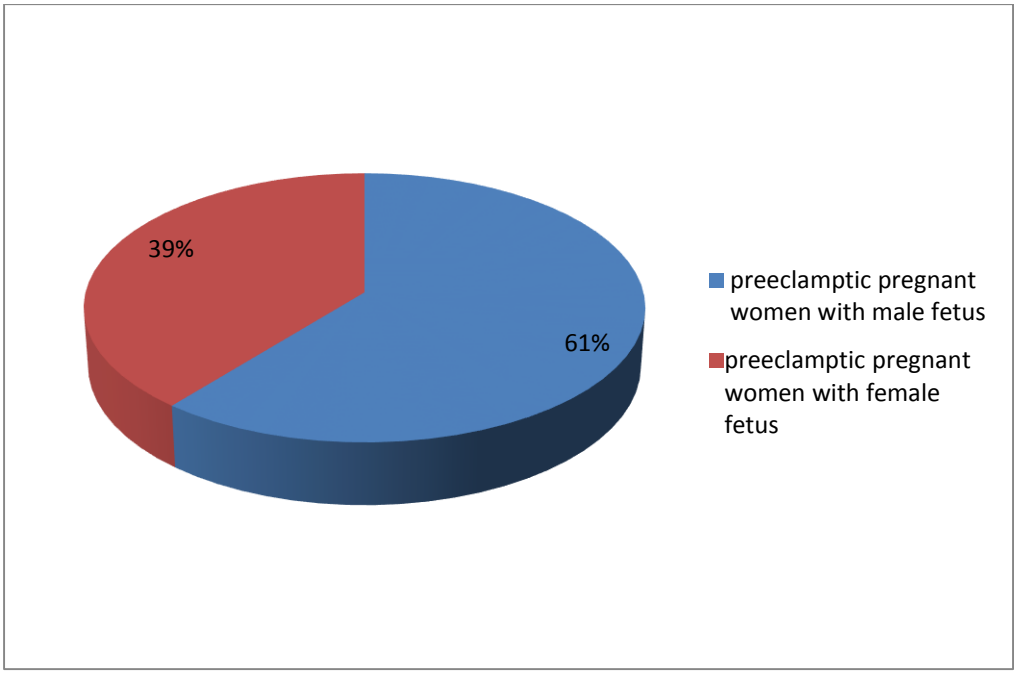

Figure 1: percentage of the preeclampsia in the pregnant women in relation to the gender of fetus

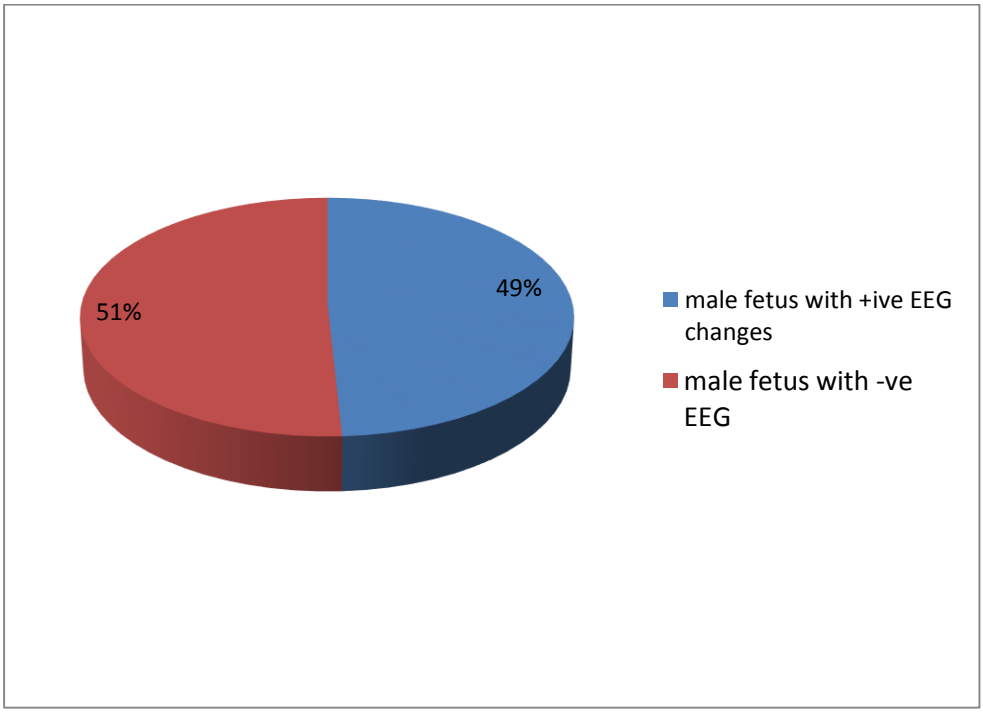

Figure 2: percentage of the EEG changes in preeclamptic pregnant women with male fetus

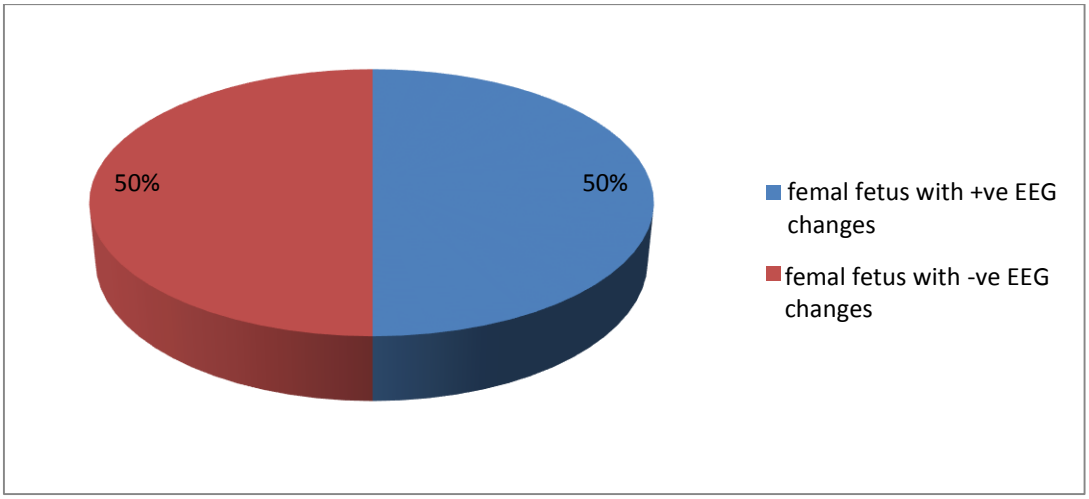

Figure 3: percentage of the EEG changes in preeclamptic pregnant women with female fetus

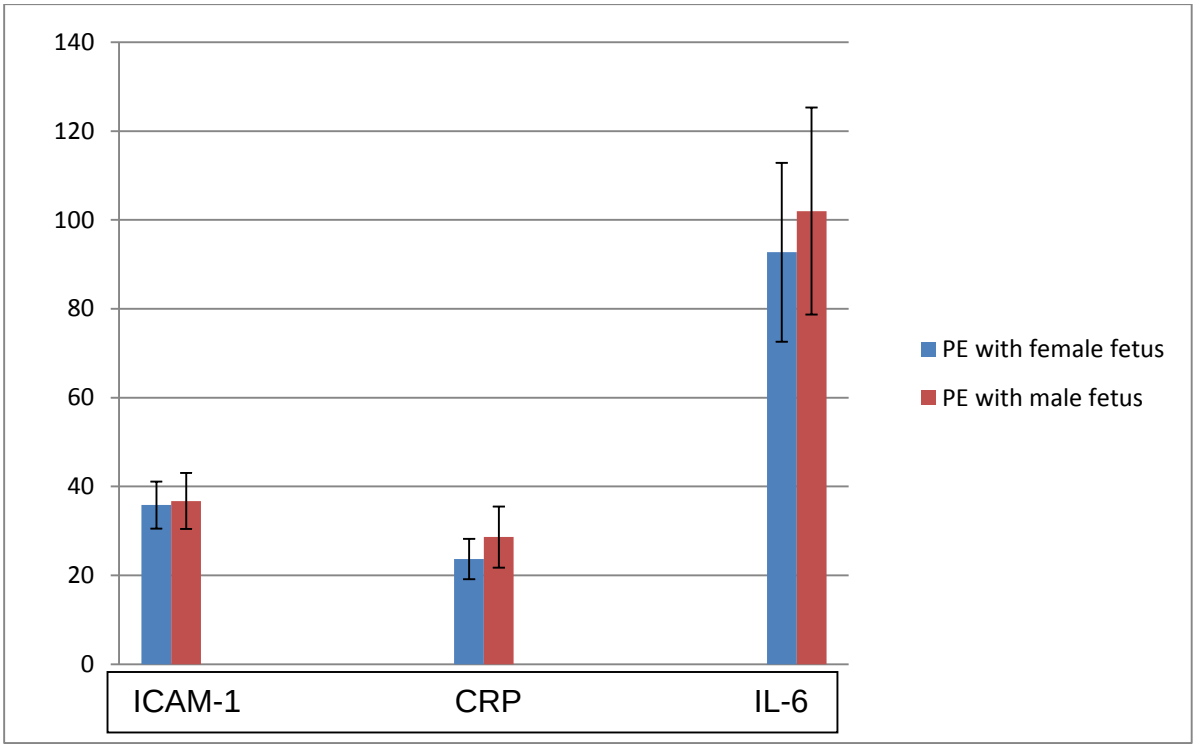

Figure 4: comparison between the values of intracellular adhesion molecules, C-reactive protein and Interleukin-6 between preeclamptic pregnant women in relation to the gender of fetus

Discussion:

Preeclampsia mean the presence of hypertension, proteinuria and nondependent edema in pregnant woman. Studies have performed to show whether fetal gender plays an important role in the development of preeclampsia. Carrying a male fetus may be regarded as having a higher risk for development of preeclampsia (Saadia and Farrukh,. 2008). Lopez also confirmed the fact that antepartum preeclampsia in singleton pregnancies occur more often in pregnancies with male

fetuses, (Lopez Llera M). Saqib reported that there is no significant association of fetal gender with eclampsia (Qureshi NS, *et al.* 2000). Antigenic disparity between the mother and fetus is likely to be heightened by a male fetus and predispose to an altered maternofetal interaction in the placental bed leading to pre-eclampsia a central pathogenic feature of the disorder (Kyong , *et al.* 1998). While Maksheed has noticed increased incidence of pre-eclampsia and pregnancy induced hypertension in primiparous mothers with female fetuses (Maksheed *et al.*, 1998).

Conclusion:

It was concluded from this study that the incidence of preeclampsia is higher when the fetus is male and there is a relationship with the serum IL-6 levels. Hormonal factor may be the cause for that.

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