

### **Discussion**

In this study the level of the potent androgen testosterone was found to be significantly higher in women with preeclampsia than in healthy controls with similar gestational age, and chronologic age as in Table 1 & Figure 1.

Several independent studies showed that androgens could cause physiologic changes strikingly similar to those seen in preeclampsia<sup>(12)</sup>. High circulating androgen concentrations (in the male range) and exogenously administered androgens have both been linked to hypertension in vivo and in vitro<sup>(6)</sup>.

Maternal serum androgen levels have been shown to be elevated in healthy pregnant women compared with levels in those who were not pregnant; this can be attributed to the increase in sex hormone binding globulin concentration induced by estrogen, or to the effect of hCG hormone which results in increasing maternal and lowering fetal testosterone<sup>(13)</sup>. Other suggestions may involve the increase in inhibin –A found in preeclamptic women which leads to increase androgen synthesis by the ovarian theca cells, with a reduction in the placental aromatization enzymes for androgens in preeclamptic women<sup>(6)</sup>.

Our findings suggest a possible effect of the enzyme deficiency, as well as a possible mechanism for its association with preeclampsia<sup>(6)</sup>.

Alternatively, it could be argued that the testosterone increase observed in the patients with preeclampsia could have been caused by decreased intravascular volume found in preeclampsia<sup>(6, 14)</sup>.

**Nitric oxide** mediates many functions of endothelium, including vasodilatation and inhibition of platelet aggregation<sup>(15)</sup>. Preeclampsia may be associated with

nitric oxide deficiency<sup>(15)</sup>, and the results of this study provide an evidence to support this hypothesis. As shown in Table 1, NO level in blood was similar in both healthy pregnant groups; it was unchanged during physiological pregnancy. During preeclampsia, the NO was decreased compared to the control level. This suggests that during preeclampsia the low activity of endothelial NO-synthases and redox-dependent transformation of NO in peroxynitrite provoke a decrease in the blood nitric oxide level<sup>(16)</sup>; these results are comparable to those of Meher & Duly<sup>(15)</sup>, Khetsuriani et al.<sup>(17)</sup>, Choi et al.<sup>(16)</sup>, and Nishikawa & Miyamoto<sup>(18)</sup>.

The reduction of NO in preeclampsia and other cardiovascular disease can be attributed to either the association of a subset of endothelial nitric oxide synthase gene (NOS3) polymorphisms (Glu298Asp, intron 4, -786>C and -786CC) with cardiovascular disease, preeclampsia and recurrence of pregnancy negative events<sup>(19,20)</sup>, or to testosterone increment in preeclampsia<sup>(15)</sup>.

Arginase is often colocalized with NOS and they maintain a complex relationship, regulating each other and competing with one another for their common substrate<sup>(21)</sup>. There is evidence that when either arginase or NOS is activated, it competitively inhibits the action of the other<sup>(21)</sup>.

During late pregnancy, arginase activity increases significantly in animals<sup>(21)</sup>. Kidney arginase was also increased in these animals<sup>(21)</sup>. This suggests that the placenta is required for maximal increase in arginase activity<sup>(21)</sup>.

Rats and sheep have also been shown to have an increase in arginase that peaks in late pregnancy<sup>(21)</sup>.