SUMMARY AND CONCLUSION

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It is widely recognized that endometrial carcinoma(EC) represents the most frequent type of genital malignancy in women . Endometrial hyperplasia(EH) has been linked with endometrial carcinoma for many years and it has since long been proposed to be a predecessor to endometrial carcinoma .

The existence of a high risk subgroup among EH patients is a well established and accepted fact today . The crucial problem is the definition of this high risk population of EH patients .

The aim of our study was to evaluate recent molecular markers : DNA ploidy status , DNA index (DI) , S- phase (SPF) and c-erbB-2 oncoprotein ; also biological marker CEA to identify their value in classifying endometrial hyperplasia into low and high risk groups and their possible role in malignant transformation .

The study group consisted of 93 women and the endometrial specimens were histopathologically classified into normal group (n = 36) (16 secretory type and 20 proliferative type), hyperplastic group (n= 50) (32 simple type and 18 complex one) and malignant group (n= 7).

The mean ± SD of age for the normal group was 41.6 ± 8.3 years for the hyperplastic 46 ± 6.1 years and for malignant cases 57 ± 9.1 years (the difference between the groups was statistically significant **P < 0.001**).

DNA analysis was made on fresh endometrial samples by **FCM** . All the normal endometrial tissues (secretory or proliferative) were **DNA** diploid (**DI** = 0.9 – 1.1) , also all cases of simple hyperplastic group showed no abnormality of DNA ploidy pattern , whereas in the complex hyperplastic group one case (6 %) was **DNA** aneuploid (**DI** = 1.7) which may represent a high risk case of an increased malignant potential. For the malignant cases 1 case (14 %) was diploid while the majority (86 %) were **DNA** aneuploid (**DI** > 1.1) .

All the seven non-diploid cases were above 40 years old and six of them were postmenopausal .

The mean ± SD **SPF** for the malignant cases (13.73 ± 6.44) was significantly higher than the normal (5.54 ± 1.73) and the hyperplastic (5.63 ± 2.50) groups (P < 0.01) , while that of hyperplastic was not significantly different from normal (P>0.05). Also non significant difference was obtained between mean **SPF** of normal secretory (5.28 ± 1.37) and normal proliferative (5.76 ± 1.9) or simple hyperplastic (5.23 ± 2.28) and complex hyperplastic (6.32 + 2.66) subgroups P>0.05).

The highest value for **SPF** in normal cases was **9 , i.e.** all normal cases ≤ **9** , whereas 12 % of hyperplastic group were **> 9** ; **2 % > 10** and no cases **> 15** . In the malignant group 71 % were **> 9** ;also **71 % > 10**

while 29 % > 15 which was statistically significant as revealed by X^2 test.

Regarding *c-erbB-2* oncoprotein expression measured in the endometrial tissue by EIA technique , the mean ± SD (HNU /μg protein) in the malignant group (3.74 ± 2.45) was significantly higher than normal group (1.47 ± 0.84) ,$P < 0.05$; but not significantly different from the hyperplastic group (2.4 ± 2.46) $P > 0.05$.

The highest value for *c-erbB-2* oncoprotein in the normal cases was 3.46 HNU / μg protein , 8 hyperplastic cases (16 %)were >3.46 HNU /μg protein and 3 malignant cases (43 %) were > 3.46 HNU / μg protein ($P<0.01$).Using a cut off value for *c-erbB-2* oncoprotein = 3.15 HNU/μg protein (mean + 2 SD) 1 (3 %) normal case was > 3.15 while 10 (20 %) hyperplastic cases and 4 (57 %) malignant cases were > 3.15 HNU /μg protein , a statistically significant difference ($P < 0.01$). From the 15 cases > 3.15 HNU /μg protein 9 (60 %) premenopausal and 6 (40 %) postmenopausal; also one (7%) was ≤ 40 years and 14 (93 %) were > 40 years .

Concerning serum CEA the mean ± SD (ng /ml) of normal group (3.72 ± 0.54) , hyperplastic (3.75 ± 0.60) and malignant (3.83 ± 0.17) which was a non significant difference .

Non significant correlation was found between age, parity, *c-erbB-2*, CEA , and SPF in the normal group while in the hyperplastic group only a positive significant correlation between parity and SPF was detected .

Whereas in the malignant group significant positive correlation between tumor grade with both **DI** and **SPF** also between **DI** and **SPF** .

From the data of the present study we could conclude that : **FCM** of cellular **DNA** content is a rapid , objective , quantitative and sensitive method to determine a highly specific and stable tumor cell marker . The utility of this technology in the evaluation of premalignant and malignant tissues (e.g. **EH** and **EC**) is becoming increasingly recognized . **DNA** analysis data by **FCM** may be useful for selecting a subset of EH patients with high risk of developing **EC** .

FCM DNA measurements (ploidy status , **DI** , and **SPF**) might add information independent of clinical and histopathological examination and might help the clinician about the decision and way of management of some cases of **EH**.

A major advantage of **FCM** measurements is that they can be done on fresh or stored (paraffin embedded) tissues as well as they are much less time consuming than other methods of **DNA** analysis.

To ascertain whether aneuploid **EH** cases represent definitely a premalignant lesions , the **DNA** results should be correlated with the final histologic and clinical follow up of patients .

In this era of rapid acceleration of knowledge of **molecular biology** in the oncologic sciences , we can expect growth factors and oncogenes to take a prominent place in molecular epidemiology and the assay of tissue and tumor virulence . These virulence factors should reduce our

complacency about the ease of curability of **EH** and **EC** and sharpen our interest in individualizing treatment of these diseases .

Measurements of ***c-erbB-2*** oncoprotein might help to detect more risky cases of **EH** since alteration in the expression of ***c-erbB-2*** oncoprotein might play an important role in malignant transformation .

Whether ***c-erbB-2*** proto-oncogene activation is actually involved in the transformation from normal to neoplastic endometrium remains to be proved. However , the presence of the ***c-erbB-2*** product in the hyperplastic endometrial tissues in amount higher than normal endometrial tissue and near to that of malignant tissue support this hypothesis in a subset of **EH** populations .

A much larger numbers of patients must be studied to determine the role and prognostic significance of ***c-erbB-2*** (and other) oncogene(s) amplification and/or overexpression in normal, hyperplastic and malignant endometrial tissues .

Clinically , this study indicates that ***molecular markers*** and biologic data must be taken into account in the management of patients with **EH** and **EC**. The more we understand about the ***molecular biology and markers***, not only in malignant tissues, but also in normal and premalignant tissues, the closer we will come to using ***molecular markers*** to their potential in diagnosis, prognosis and therapeutic management of cancer patients .

Ultimately , our future treatment might include a form of ***gene therapy*** or be directed at inhibitors of growth factors and oncoproteins that might have some role in malignant transformation .