CYTOPATHOLOGY OF THE ENDOMETRIUM BEFORE AND AFTER ANTI-OESTROGEN MEDICATION IN DIFFERENT AGE GROUPS

THESIS
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بسم الله الرحمن الرحيم

نَرفَعُ دَرَجٰتٍ مَّن نَّشَـــاَءُ وَ فَوقَ
كُلِّ ذِى عِلمٍ عَلِيمٌ

صدق الله العظيم
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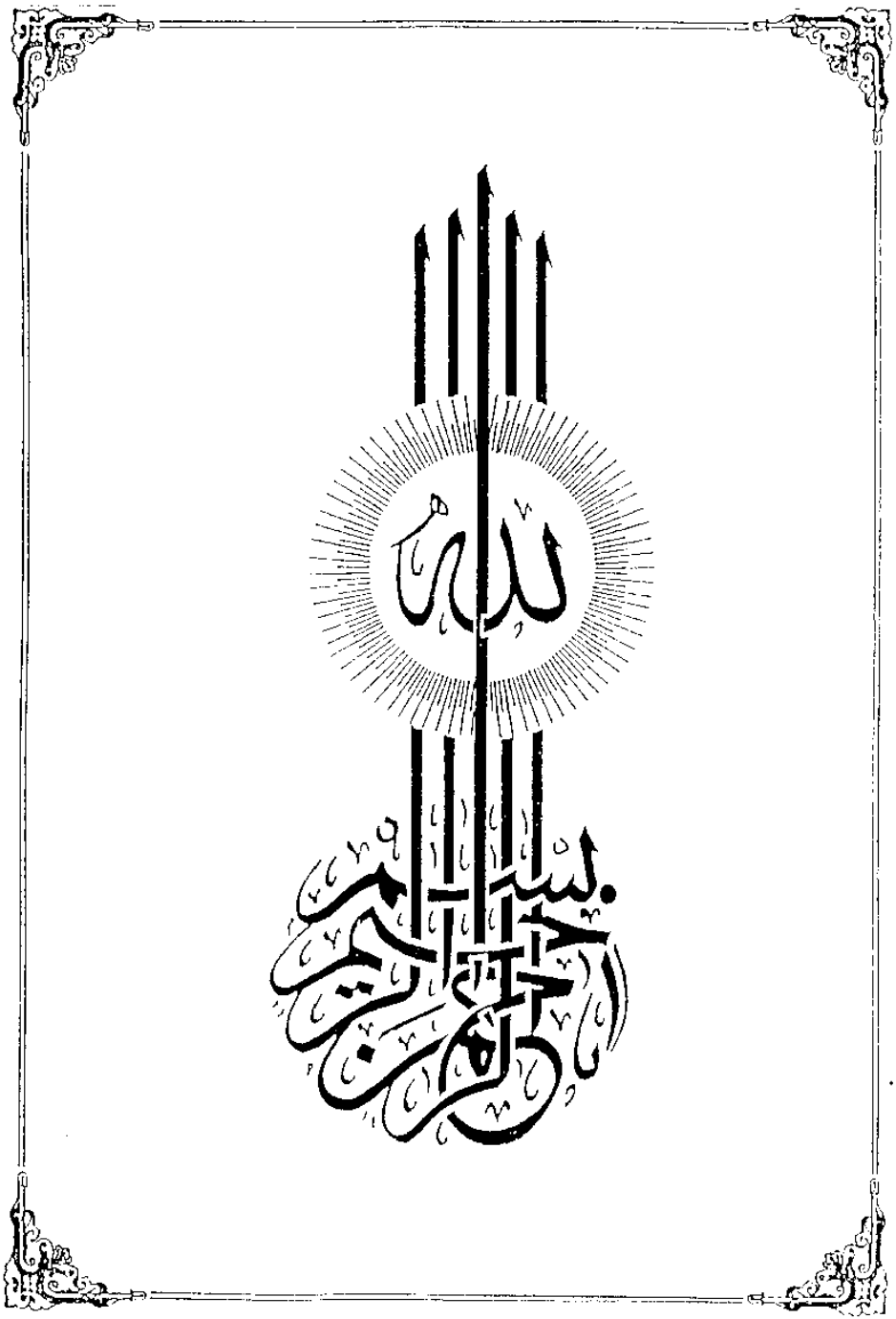

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Introduction

INTRODUCTION

There has been a relative lack of interest in endometrial cancer by oncologist for many years, because of its apparently low incidence, relatively low virulence, and correspondingly low mortality rate, relative to other cancers.

Interest in endometrial cancer increasing nowadays, because of its increased frequency, and its hormonal relationship. It is a disease of age with a peak incidence ranging between 58 - 60 years, which is ten years later than the peak incidence of adenomatous hyperplasia (Gusberg and Kaplan, 1963).

Nowadays with the increase in life expectancy, (more than seventy five years) (Korenman et al., 1978) , it has become the most common cancer of female genital tract, especially in United States.

An association between endometrial hyperplasia and subsequent carcinoma has been amply documented, since it was first noted by Baker in 1904 (Hertig and Sommers, 1949; Kistner et al., 1966; Wentz, 1974; and Sherman, 1978).

Much of the present day confusion about the significance of the various forms of hyperplasia stems from the different interpretations of the widely used terms , " adenomatous hyperplasia", " atypical hyperplasia" and "carcinoma in situ".

Precancerous lesions of the endometrium, fall into two general categories of widely different significance : Cystic hyperplasia and heterogenous group of Complex hyperplasia. These lesions may be generalised or localised. They are sometimes present within an endometrial polyp (Welch, 1977).

The relation between hormones and endometrial cancer has been the subject of investigations for many years, and has been reviewed by a number of investigators. (Larson, 1954; Andrews, 1961 and Gusberg, 1967).

Larson, (1954), was able to formulate five distinctly different points of view, held by various groups of investigators. Briefly, these are as follows:

1- Endometrial hyperplasia (and hence excess oestrogen stimulation) predisposes to carcinoma at any age.

2- Endometrial hyperplasia and cancer are not associated, but the unopposed action of oestrogen with its resultant effect on the endometrium, is the basic principle in the development of endometrial carcinoma.

This especially goes for the individuals who posses the genetic factor necessary for the development of cancer.

3- Endometrial hyperplasia may be followed by anaplasia, carcinoma in situ, and endometrial adenocarcinoma but, no convincing studies are available to show that oestrogen stimulation alone will produce this picture.

4- Neither hyperplasia nor prolonged oestrogen stimulation can be associated with endometrial cancer, except by mere chance.

5- Endometrial hyperplasia, may predispose to malignancy, when it occurs as a result of postmenopausal oestrogenic stimulation.

Oestrogen stimulation of the endometrium, unopposed by progesterone, can produce a progression of changes from benign proliferation to atypical hyperplasia and adenocarcinoma of the endometrium (Gusberg, 1967).

It is possible now to identify high risk individuals and to detect early stage changes of endometrial cancer through examination of curettage and aspiration biopsy specimens. Application of these approaches will contribute to the prevention of invasive and advanced endometrial carcinoma (Gusberg and Mulvihill, 1986).

Several of the risk factors associated with endometrial cancer are also risk factors for breast cancer (high oestrogen production, anovulation). The occurence of the cancers themselves are associated and the epidemiology of breast cancer clearly indicates that sex hormones play a central part (Gusberg and Mulvihill, 1986).

The demonstration of oestrogen and progesterone receptors in endometrial carcinoma and the finding that approximately one third of the tumours respond to endocrine therapy naturally has led to clinical trials with "Tamoxifen", a non steroidel antiestrogen used with great success in the treatment of breast cancer (Jordan, 1986).

AIM OF THE WORK

The aim of this work was to study and evaluate, the effects of antiestrogen medication "Tamoxifen" on the endometrium which was the seat of endometrial hyperplasia, and carcinoma, as they are partly the end result of a continuous oestrogen effect on the endometrium.

The purpose is to spare the patients especially young ones , the physiological and psychological drawbacks of a major operation like hysterectomy done as a first choice treatment for the patients nowadays especially in cases of "atypical hyperplasia - carcinoma in situ" and stage I well differentiated adenocarcinoma.

This trial will be carried out in different age groups to evaluate the difference between them in response to the drug.

The endometrium will be assessed both cytologically by endometrial aspiration specimens, and histologically by endometrial biopsy.

A correlation between both methods will be done, in a trial to evaluate endometrial cytology as an easier technique for endometrial sampling and its study, compared to curettage and histopathologic diagnosis. Efficacy of endometrial cytology as a method of diagnosis especially in high risk group, could then be generalised as an outpatient routine procedure, instead of hospitalization for dilatation and curettage (D & C).

The study of cervicovaginal smear will be also done for patients, to study its efficiency in detection of endometrial pathology, and to rule out cervical causes of bleeding.

The Karyopyknotic (K.I) index which is a reflection of the oestrogen impregnation of the patient will be studied, before and after use of Tamoxifen. This study will enable us to determine the effect of the drug (antioestrogen) whether agonistic or antagonistic on the squamous cells maturation which is totally oestrogen dependent. Its determination may be also a rough indictor of the oestrogen receptors ER content of the tumour studied as ER tumour content is inversly related to K.I in postmenopausal women.

Review of Literature

TERMINOLOGY AND CLASSIFICATION OF PRECANCEROUS ENDOMERTIAL LESIONS

Precancerous lesions fall into two general categories of widely differing significance : Cystic hyperplasia and a heterogeneous group of Complex hyperplasias. These lesions may be generalized or localized, sometimes within an endometrial polyp (Welch and Scully, 1977).

Little controversy exists about the usage of the term "cystic" for the very common form of Swiss-cheese hyperplasia that is clearly related to continous unopposed oestrogen stimulation. In contrast, there has been considerable disagreement about the terminology of the more important complex hyperplasias, which involve alterations on the pathway to carcinoma both in the architecture and proximity of the glands and their lining epithelium (Scully, 1982).

Much of the present days confusion about the significance of the various forms of complex hyperplasia stems from differing interpretations of the widely used terms: "adenomatous hyperplasia", "atypical hyperplasia", and "carcinoma in situ".

Gusberg (1947), introduced the designation "adenomatous hyperplasia" to include the entire spectrum of precancerous architectural and cytological abnormalities of the endometrium, with subcategories to mild, moderate and severe with the exception of cystic hyperplasia.

The most severe lesion within the Gusberg spectrum of adenomatous hyperplasia was called