Diagnostic accuracy of serum LDH and TVUS in detecting endometrial cancer in women with postmenopausal bleeding

Thesis
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By
Mohamed Rasheed Baraka
(M.B., B.Ch)

Supervised by

Prof. Dr. Tarek Fawzy
Professor of Obstetrics and Gynecology
Faculty of medicine – Cairo University

Dr. Sherif Negm
Assistant Professor of Obstetrics and Gynecology
Faculty of Medicine – Cairo University

Dr. Maryam Abdelnaby
Lecturer of Obstetrics and Gynecology
Faculty of Medicine – Cairo University

Faculty of Medicine
Cairo University
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Abstract

Objective: to evaluate the diagnostic accuracy of serum LDH and TVS in the detection of endometrial cancer in women with postmenopausal bleeding.
Methodology: 100 cases with postmenopausal bleeding were scanned using TVS to measure endometrial thickness and serum LDH was measured.
Results: A cutoff of 5mm endometrial thickness showed a sensitivity of 93% and specificity of 60%, while adopting a cutoff of 420U/L for serum LDH has a sensitivity of 100% and a specificity of 60%.
Conclusion: Serum LDH can be used as a good negative test to exclude endometrial cancer in women with postmenopausal bleeding.

Key word: TVUS , LDH , bleeding , postmenopausal

Contents

Introduction

Postmenopausal bleeding occurs in approximately 3% of postmenopausal women and it is the usual presenting symptom of endometrial carcinoma in approximately 93% of cases. About 5-15% of postmenopausal women with abnormal bleeding may have endometrial cancer ***(Anonymous, 2007)***. Therefore; a reliable and minimally invasive method is needed to identify those cases.

Transvaginal ultrasonography (TVUS) has become a common method to monitor endometrial thickness in particular in cases of postmenopausal bleeding with sensitivity of 80-100% if a level of 5mm is used as a cut-off ***(Bostis et al., 1992)***, ***(Nasri et al., 1991)***. However, specificity of TVUS is low, partly because of other reasons for thick endometrium like hormone replacement therapy and partly because the endometrium might not be clearly identified due to myometrial echoes. Furthermore, in patients with thick endometrium or inconclusive findings, there is a need for further confirmation of hyperplasia, chronic endometritis or tumors usually by histology.

Lactate dehydrogenase (LDH) is a major enzyme involved in glycolysis when oxygen resources are reduced. Under anaerobic conditions the pyruvate produced from

glucose, instead of entering the Krebs cycle, becomes converted into lactate by the catalytic activity of LDH ***(Holbrook et al., 1975)***.

The tumor environment is highly hypoxic so that cancer cells have an intensified anaerobic metabolism ***(Harris et al., 2002)***. Furthermore, stabilization or overexpression of the transcription factor hypoxia-inducible factor 1a (HIF 1a) in cancer cells occurs, leading to the up-regulation of lactate dehydrogenase A (LDHA) gene ***(Elstrom et al., 2004) (Laughner et al., 2001), (Semenza et al., 1996)***.

LDH is increased in the serum of a fraction of cancer patients, a feature closely related to prognosis ***(Argiris et al., 2001), (Brizel et al., 2001), (Kemeny et al., 1989)***.

Aim of the Work

To evaluate the diagnostic accuracy of serum lactate dehydrogenase and transvaginal sonography in detection of endometrial carcinoma in women with postmenopausal bleeding.

CHAPTER (1)

Postmenopausal Bleeding

The terms menopause and climacteric are often used loosely and interchangeably but strictly apply to two different periods at the end of reproductive life of human female.

Climacteric is derived from the Greek Klimakter (the rung of the ladder) and means critical period in human life where declining ovarian function marks the loss of reproductive potential, and is applied to the 5-15 years before the menopause. Menopause is derived from the Greek Men (month) and Pauo (to stop) and is applied to the permanent cessation of menstruation due to loss of ovarian follicular activity ***(Davey, 1995)***.

Menopause is considered to have occurred retrospectively after one year of amenorrhea ***(Brincat and Studd, 1988)***.

Demography:

The ages of 45 and 55 may be regarded as the approximate 5% and 95% confidence limits for the age of menopause. The age limits of 40 and 60 years commonly

quoted for the diagnosis of premature and late menopause represent the extremes of the range and are well outside the normal range ***(Davey, 1995)***.

A number of factors appear to determine the onset of menopause. Multiparty and increased body mass index (BMI) are associated with later onset ***(Hardy and Kuh, 1999)***, whereas smoking ***(Windham, 1999)***, nulliparity, medically treated depression ***(Harlow, 1995)***, toxic chemical exposure, and treatment of childhood cancer with abdominal -pelvic radiation and alkylating agents have been associated with a younger age at onset ***(Silbergeld and Flaws, 1999)***. Premature or early menopause (age below 40) has been linked to both familial and nonfamilial X-chromosome abnormalities ***(Uzilleli et al., 1999)***.

Postmenopausal bleeding is defined as uterine bleeding that occurs after 1 year of amenorrhea in a woman who is not receiving hormone replacement therapy ***(Nasri and Coast, 1989)***. Women on continuous progesterone and estrogen hormone therapy can expect to have irregular vaginal bleeding, especially for the first 6 months. This bleeding should cease after 1 year. Women on estrogen and cyclical progesterone should have a regular withdrawal bleeding after stopping the progesterone ***(Abeloff, 2000)***.

Postmenopausal bleeding is a common clinical problem accounting for approximately 5% of office visits to a general gynecologist ***(Dubinsky et al., 1999)***.

Postmenopausal bleeding should always be investigated, because it could be a sign of endometrial carcinoma, which has a much higher cure rate if diagnosed early. Early diagnosis is important because the 5-year survival varies from 90 to 100% in patients with little or no myometrial involvement, to 40 to60% in patients with deep myometrial invasion ***(Chen and Lee, 1983; Di Saia et al., 1985; Figge et al., 1985)***.

It is estimated that endometrial carcinoma is the cause of postmenopausal bleeding in 10% of cases ***(Creinin, 1998)***.

Causes of postmenopausal bleeding:

1-Atrophic endometrium:

Atrophic endometrium is the most common cause of postmenopausal bleeding, accounting to up to 82% of postmenopausal women biopsied for vaginal spotting or bleeding ***(Choo et al., 1985)***.

Bleeding associated with atrophy is manifested by vaginal spotting resulting from no or minimal estrogenic stimulation of the endometrium. Simple atrophy alone is

not always the cause of postmenopausal bleeding however other factors have been claimed, such as chronic non specific endometritis leading to local tissue necrosis and bleeding. Chronic endometritis however occurs infrequently and this is observed in only 6% of patients who had atrophic endometrium ***(Choo et al., 1985)***.

2-Endometritis:

- Chronic Non specific endometritis:

After menopause, the endometrium may undergo shrinkage becoming thin and atrophic. The thinned out atrophic mucosa is prone to superficial punctuate ulceration and infection ***(Goldstein, 1990)***.

The infected epithelium exudes pus, which tend to collect in the uterus to form a pyometra. Sometimes in response to pyometra, the endometrium undergoes metaplasia ***(Tindall, 1987)***.

- Chronic specific endometritis:

A- Tuberculous endometritis:

The endometrium is affected in about 50-75% of patients with genital tuberculosis during reproductive years, and can be also affected in postmenopausal women. The denuded surface of the postmenopausal endometrium is

especially susceptible to infection by the organism, which reaches the endometrium secondary to tubal infection ***(Mac Intosh and Saxon, 1985)***.

B- Sarcoidosis:

Few cases of sarcoidosis had endometrial involvement in association with the systemic disease ***(Hoku, 1987)***.

C- Viral infections:

Herpes virus, cytomegalovirus and human papilloma virus are the only viruses known to infect the endometrium ***(Venkataeshen, 1985)***.

3-Iatrogenic:

- Estrogen and progesterone therapy:

Unopposed estrogen causes reproducible changes in the postmenopausal endometrium. The most remarkable are present in the epithelium, which becomes taller and crowded. Nuclear activity, including mitosis increases, and greater numbers of estrogen and progesterone receptors have been documented.

These responses may eventuate in the pathologic states, including endometrial hyperplasia, characterized by excessive amounts of tissue with effusive complexly

budding gland patterns. A fast progression from postmenopausal atrophy to carcinoma may be observed in 2 to 3 years in some users instead of 10 years or more in non users ***(Healy and Hodgan, 1983; Rosenwaks et al., 1979; Voigt et al., 1991)***.

Progesterone in the postmenopausal patient is inhibitory to the proliferative effect of estrogen and productive of unique histological and ultra structural features. The administration of sufficient amounts of progesterone in cyclic fashion reduces the risk of endometrial pathology associated with unopposed estrogen exposure. Withdrawal from estrogen or from progesterone following estrogen priming results in dissolution of the superficial endometrial striata, with resultant bleeding ***(Whitehead et al., 1981)***.

- Tamoxifen:

Tamoxifen is a nonsteroidal estrogen antagonist that has some agonistic properties. It is used in the treatment and protection against breast cancer. It inhibits breast cancer but, paradoxically stimulates endometrial growth, suggesting a tissue-specific action ***(Neven, 1993)***.

4- Endometrial polyps:

Polyps occur relatively frequently after the menopause. The prevalence of polyps in the general population is about 24%. The most common clinical presentation is abnormal vaginal bleeding. Endometrial polyps occur singly in about 3/4 of cases. Although they may occur at any location within the endometrial cavity, they are found most often in the fundus, particularly in the corneal areas ***(Kurman and Mazur, 1994)***. They range from barely perceptible lesions less than a few millimeters in diameter to large masses that occupy the entire endometrial cavity and simulate cancer ***(Lawrence and Skully, 1989)***.

5- Endometrial hyperplasia:

Endometrial hyperplasia is defined as a proliferation of glands of irregular size and shape with an increase in the gland/stroma ratio compared with proliferative endometrium ***(Gambrell, 1997)***. Postmenopausal women who develop hyperplasia are almost invariably, manifested by abnormal bleeding. Typically, women with hyperplasia or carcinoma have moderate or heavy vaginal bleeding compared with women with atrophic endometria who present with spotting ***(Kurman and Norris, 1994)***.

6- Metaplasia:

Metaplasia is defined as the replacement of atypical endometrial epithelium by another type not normally found in the endometrium. Metaplasia may occur in association with various benign conditions as polypi, endometritis and hyperplasia. The presence of metaplasia with hyperplasia may produce dramatic alteration that can be confused microscopically with carcinoma. The frequent association of endometrial metaplasia and hyperplasia is probably due to the fact that both are often associated with hyperestrogenic state ***(Hendrickson and Kempson, 1990)***.

7- Endometrial cancer:

Uterine cancer is the fourth commonest cancer in women and is the commonest cancer of the female genital tract. Endometrial cancer is the seventh leading cause of death from malignancy in females. Endometrial cancer is the most common type of cancer of the corpus uteri constituting about 95% of all malignant lesions of the uterine cavity ***(Smith et al., 2001; Silverberg et al., 1990; Miller et al., 1993)***.

CHAPTER (2)
Endometrial Cancer

Introduction:

Cancer of the endometrium is the second commonest gynecological tumour reported in the United Kingdom (UK) but in the European Union (EU) as a whole it ranks above ovarian cancer as the commonest tumour. The overall incidence in developed countries has risen in recent years. The death rate, around 20% overall, is lower than that of other gynaecological cancers, due principally to early presentation by means of post-menopausal bleeding. There are no practical preventative strategies currently available, so changes in incidence generally reflect demographic and lifestyle changes.

Treatment has remained relatively unchanged over the last 40 years relying principally on surgery to achieve cure. During the last 10 years interest in endometrial cancer has increased considerably and investigations into the optimal use of adjuvant radiotherapy, the effect of tamoxifen, the role of chemotherapy, the effectiveness of lymphadenectomy, genetic predisposition to the disease and the influence of less common histotypes have all