Serum prolactin level for early predection of precancerous and endometrial carcinoma in cases of perimenopausal and postmenopausal abnormal uterine bleeding

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Abstract: Introduction: Endometrial adenocarcinoma is the most common malignant neoplasm of the female genital tract comprising 6% of female cancers**. Aim of the work:** To develop a risk prediction model to see is there role of serum prolactin level and early predection of precancerous and endomertrial carcinoma in perimenopausal and postmenopausal abnormal uterine bleeding. **Material and Method:** This study was conducted on 200 Patients referred to one of the participating centres because suffering of perimenopausal and postmenopausal bleeding. 100 cases with perimenpasual bleeding and 100 cases with post menepasual abnormal uterine bleeding. **Results:** In our study age distribution of premenopausal patients is mostly between 40-45 years (60%) and age distribution of postmenopausal patients is between 50-55 years (70%). Most of the patients perimenopausal patients in the study multiparous (95%) and the same in postmenopausal patients in the study multiparous (93%). **Conclusion:** The level of prolactin varies according to the type of AUB. Majority of the participants had prolactin level within the normal range. Around 25% of the participants had prolactin level above normal level in perimenpausal patients and 16%of postmenpausal patients.

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1. Introduction

Endometrial adenocarcinoma is the most common malignant neoplasm of the female genital tract comprising 6% of female cancers. Despite the advances that have been made in other cancers, both annual incidence of and death rate associated with endometrial cancer appear to be rising (1). Endometrial cancer, which originates from the lining of the uterus, accounts for approximately 90% of uterine cancers. The incidence of endometrial cancer in women in the U.S. is 2–3%. According to the American Cancer Society, the incidence peaks between the ages of 60 and 70 years, but 10–25% of cases may occur before the age of 50 (2). Increased risk of developing endometrial cancer has been noted in women who take tamoxifen and women with genetic susceptibility to the disease (3). Continuing challenges of endometrial cancer treatment include the need to improve screening and prevention efforts. The 5-year survival for early stage localized endometrial cancer is 75–95% however prognosis is poor for cancers found at stages III–IV. Five-year survival rate falls to 66% if cancer has spread regionally at the time of diagnosis. For women with disease that has spread beyond pelvis (stage IV) survival is less than 20% (3). Results from pelvic examination are frequently normal, especially in the early stages of disease, thus limiting the ability to identify early disease. Changes in size, shape or consistency of the uterus and/or its surrounding supporting structures may exist when the disease is more advanced. Although not recommended as a general screening test, the American Cancer Society does advocate endometrial sampling or biopsy in high-risk women at the time of menopause (4). CA 125 correlates with tumor size and stage of endometrial cancer (5) and is also a significant independent predictor of the extrauterine spread of disease (6). At present, no serum biomarkers are available for screening for endometrial carcinoma or for monitoring recurrence in endometrial carcinoma survivors. Patients with recurrent disease are detected only following the development of symptoms or abnormalities in imaging assessments (7). The Adnex risk model can be used by medical doctors to diagnose ovarian cancer in women who have at least one persistent adnexal (ovarian, para-ovarian, and tubal) tumour and are considered to require surgery The Adnex paper uses nine predictors. There are three clinical variables, age, serum CA-125 level, and type of centre (oncology referral centrevs other), and six ultrasound variables, maximal diameter of lesion, proportion of solid tissue, more than 10 cyst locules,

number of papillary projections, acoustic shadows, and ascites. All patients included required surgery as judged by a local clinician. As with all current diagnostic models for adnexal tumours (e.g. IOTA models, RMI, ROMA) it implies that patients selected for expectant management were excluded (8).

Aim of the work

To develop a risk prediction model to see is there role of serum prolactin level and early predection of precancerous and endomertrial carcinoma in perimenopausal and postmenopausal abnormal uterine bleeding.

2. Materials and methods

This study was conducted on 200 Patients referred to one of the participating centres because suffering of perimenopausal and postmenopausal bleeding.

100 cases with perimenpasual bleeding and 100 cases with post menepasual abnormal uterine bleeding.

Examination

1-History 2- General examination.

3-Local examination 4- Ultrasound examination.

5- Serum prolactin6- Serum CA1257- fractional dilatation and curettage biobsy.

8- Hisopathological examination.

Inclusion criteria

1-Age above 40years old.

2-Not have genral cause of bleeding.3- no history of drugs that increase serum prolactin. Then we claculted the model score as the following:

- Age one point if the case perimenopausal tow points if the case postmenopausal.
- Transvaginal Ultrasound examination for endometrial thickness.
- Serum prolactin. The model index.

Age score x endometrial thickness/mm x serum prolactin.

Then we compared the result by histopathlogical examination after d & cbiobsy.

Sensitivity and specificity was tested.

3. Result

Age distribution of premenopausal patients

Age in years	No.of cases	Percentage
40-45	60	60%
46-50	37	37%
>51	3	3%
Total	100	100%

Most of the patients in the study between 40-45 years (60%)

Age distribution of postmenopausal patients

Age in years	No. of cases	Percentage
50-55	70	70%
56-60	37	23%
>61	7	7%
Total	100	100%

Most of the patients in the study between 50-55 years (70%)

Parity in premenopausal patient

Parity	No. of cases	Percentage
Nulliparous	5	5%
Multiparous	95	95%
Total	100	100%

Most of the patients perimenopausal patients in the study multiparous (95%)

Parity in postmenopausal patients

Parity	No. of cases	Percentage
Nulliparous	7	7%
Multiparous	93	93%
Total	100	100%

Most of the patients postmenopausal patients in the study multiparous (93%)

Previos delivery

Delivery	No. of cases	Percentage
None	7	7%
Normal vaginal	89	89%
Caesarean section	4	4%
Total	100	100%

Most of the Previos delivery of postmenopausal patients in the study normal vaginal delivery (89%).

Previos delivery

Delivery	No. of cases	Percentage
None	5	5%
Normal vaginal	85	85%
Caesarean section	10	10%
Total	100	100%

Most of the Previos delivery of perimenopausal patients in the study normal vaginal delivery (85%).

Medical history in perimenopausal patients

Type	No.of cases	Percentage
None	48	48%
DM	24	24%
HTN	20	20%
Hepatic	6	6%
Renal	1	1%
Pulmonary	1	1%

DM and HTN are important risk factor in perimenopausal patients in this study

Medical history in postmenopausal patients

Type	No.of cases	Percentage
None	48	48%
DM	19	19%
HTN	22	22%
Hepatic	8	8%
Renal	1	1%
Pulmonary	2	2%

DM and HTN are important risk factor in postmenopausal patients in this study

Histopathology of Endometrium

Histopathology of Endometrium	No.of cases	Percentage
Proliferative endometrium	29	29%
Atrophic endometrium	3	3%
Endometrial hyperplesia	48	48%
Endometrial cancer	4	4%
Endometrial polyp	16	16%
Total	100	100%

Most of the perimenopusal patient in this study have endometrial hyperplesia (48%) followed by proliferative endometrium (29%)

Histopathology of Endometrium

Histopathology of Endometrium	No.of cases	Percentage
Atrophic endometrium	40	40%
Endometrial hyperplesia	30	30%
Endometrial cancer	7	7%
Endometrial polyp	23	23%
Total	100	100%

Most of the postmenopusal patient in this study have Atrophic endometrium (40%) followed by endometrial hyperplesia (30%).

Thickness of endometrium

Thickness of endometrim (mm)	No.of cases
Less than 4mm	4
4-8 mm	35
8-15mm	45
>15	16
Total	100

45 perimenopausal patients (45%) have thickness of endometrium between 8-15 mm followed by 35 patients (35) have thickness of endometrium between 4-8mm

Thickness of endometrium

Thickness of endometrim (mm)	No.of cases
Less than 5mm	42
5-10mm	20
10-15mm	14
15-20mm	13
≤20mm	11
Total	100

42 postmenopausal patients (42%) have thickness of endometrium less than 5 mm followed by 20 patients (20%) have thickness of endometrium between 5-10 mm.

Descriptive analysis ofofperimenopausal Group 1

	endometrial thickness	serum prolactin	Serum CA-125	score
Mean	10.82	27.91	16.87	339.73
Standard Deviation	4.363253	18.39417	11.0423	378.9468
Range	19	113	59	2594
Minimum	3	6	6	24
Maximum	22	119	65	2618

Descriptive analysis ofpostmenopausal Group 2

	endometrial thickness	serum prolactin	Serum CA-125	Score
Mean	10.43	21.72	18.71	515
Standard Deviation	6.570911	15.54081	12.39118	700.4018
Range	21	81	59	4112
Minimum	4	6	6	64
Maximum	25	87	65	4176

4. Discussion

In our study age distribution of premenopausal patients is mostly between 40-45 years (60%) and age distribution of postmenopausal patients is between 50-55 years (70%). Most of the patients perimenopausal patients in the study multiparous (95%) and the same in in postmenopausal patients in the study multiparous (93%). Most of the previos delivery of postmenopausal patients in the study normal vaginal delivery (89%). and normal vaginal delivery in of premenopausal patients in the study (85%). Dmand Htn are important risk factor in perimenopausal patients in this study dm is (24%) in all cases and htn is (20%) and in postmenopausal patients in this study dm is (19%), htn is (22%). In histopathology of endometrium most of the perimenopusal patient in this study have endometrial hyperplesia (48%) followed by proliferative endometrium (29%), endometrial polyp in (16%), endometrial cancer in (4%) lastly atrophic endometrium in (3%). Most of the postmenopusal patient in this study have atrophic endometrium (40%) followed by endometrial hyperplesia (30%), endometrial polyp (23%) and endometrial cancer (7%). In thickness of endometrium 45 perimenopausal patients (45%) have thickness of endometrium between 8-15 mm followed by 35 patients (35) have thickness of endometrium between 4-8mm and more than 15 mm is (16%) and less than4mm is (4%). In Postmenopausal patients (42%) have thickness of endometrium less than 5 mm followed by 20 patients (20%) have thickness of endometrium between 5-10 mm and more than 20 mm (11%). Serum prolactin were calculated assuming that the histopathlogical examination after d & cbiobsy is the gold standard test, and the serum prolactin value =

(35 iu/ml) was used in our study as a cutoff point for diagnosis of proliferative endometrium. The probability that a diseased subject shows a positive test using serum prolactin = 18.75 %. Sensitivity and specificity values for serum ca-125were calculated assuming that histopathlogical examination after d & cbiobsy is the gold standard test, and the serum ca-125value = (37 iu/ml) was used in our study as a cutoff point for diagnosis of proliferative endometrium so it is not suitable to estimate sensitivity of ca-125 in perimenopausal patients. There was a positive correlation between serum prolactin and serum ca-125 in the proliferative endometrium in group 1perimenopausal patients with correlation coefficient (r) = 0. 618082. There was a positive correlation between serum prolactin and endometrial thickness in the proliferative endometrium in group 1 perimenopausal patients with correlation coefficient (r) = 0. 622214. There was a positive correlation between endometrial thickness and ca 125 in the proliferative endometrium in group perimenopausal patients 1 with correlation coefficient (r) = 0. 388593. The probability that endometrial hyperplesia shows a positive test using serum prolactin = 31.25 % in group perimenopausal patients. The probability that endometrial hyperplesia shows a positive test using serum ca 125 = 10.41 %. In group perimenopausal patients. There was a positive correlation between serum prolactin and serum ca-125 in the endometrial hyperplasia in group 1 with correlation coefficient (r) = 0. 210034. There was a positive correlation between serum prolactin and endometrial thickness in the endometrial hyperplasia in group 1 with correlation coefficient (r) = 0. 101458. There was a positive correlation between endometrial thickness and ca 125 in the endometrial hyperplasia in group 1 with correlation coefficient (r) = 0. 062084. In the group perimenopausal patients 1, all cases in atrophic endometrium are diseased so it is not suitable to estimate specificity of serum prolactin due to absence of free cases. In the group perimenopausal patients 1, all cases in atrophic endometrium are diseased so it is not suitable to estimate specificity of serum ca-125due to absence of free cases. There was no correlation between serum prolactin and serum ca-125 in the atrophic endometrium in group perimenopausal patients 1 with correlation coefficient (r) = 0. The probability that endometrial polyp shows a positive test using serum prolactin = 20.68 % in group perimenopausal patients. The probability that a endometrial polyp shows a positive test using serum ca 125 = 10.34 % in group perimenopausal patients. There was a positive correlation between serum prolactin and serum ca-125in the endometrial polyp in group 1 with correlation coefficient (r) = 0. 288493. There was a positive correlation between serum prolactin and endometrial thickness in the endometrial polyp in group 1 with correlation coefficient (r) = 0. 170834. There was a positive correlation between endometrial thickness and serum ca 125 in the endometrial polyp in group 1 with correlation coefficient (r) = 0. 004976. The probability that a endometrial cancer shows a positive test using serum prolactin = 100 %. In group perimenopausal patients. The probability that a diseased subject shows a positive test using serum ca 125 = 50 %. In group perimenopausal patients. There was a negative correlation between serum prolactin and serum ca-125 in the endometrial cancer in group 1 with correlation coefficient (r) = -0. 68813. There was a positive correlation between serum prolactin and endometrial thickness in the endometrial cancer in group 1 with correlation coefficient (r) = 0. 825142. There was a negative correlation between endometrial thickness and serum ca 125 in the endometrial cancer in group 1 with correlation coefficient (r) = -0. 917. The probability that endometrial hyperplasia in group 2 postmenopausal patients shows a positive test using serum prolactin = 13.33 %. The probability that a endometrial hyperplasia in group 2 postmenopausal patients shows a positive test using serum ca 125 = 6.66 %. There was a positive correlation between serum prolactin and serum ca-125 in the endometrial hyperplasia in group 2 with correlation coefficient (r) = 0. 131947. There was a positive correlation between serum prolactin and endometrial thickness in the endometrial hyperplasia in group 2 with correlation coefficient (r) = 0. 101458. There was a positive correlation between endometrial thickness and ca 125 in the endometrial hyperplasia in group 2 with correlation coefficient (r) = 0. 062084. The probability of atrophic endometrium in group 2subject shows a positive test using serum prolactin = 12.50 %. The probability that a atrophic endometrium in group 2shows a positive test using serum ca 125 = 7.50 %. There was a positive correlation between serum prolactin and serum ca-125 in the atrophic endometrium in group 2 with correlation coefficient (r) = 0.085219. There was a negative correlation between serum prolactin and endometrial thickness in the atrophic endometrium in group 2 with correlation coefficient (r) = -0.06956. There was a negative correlation between serum prolactin and serum ca-125 in the atrophic endometrium in group 2 with correlation coefficient (r) = -0.0602. The probability that of endometrial polyp in group 2 shows a positive test using serum prolactin = 13.04 %. The probability that endometrial polyp in group 2 shows a positive test using serum ca 125 = 9.52 %. There was a positive correlation between serum prolactin and serum ca-125 in the endometrial polyp in group 2 with correlation coefficient (r) = 0. 222535. There was a

negative correlation between serum prolactin and endometrial thickness in the endometrial polyp in group 2with correlation coefficient (r) = 0. 170834. There was a negative correlation between endometrial thickness and ca 125 in the endometrial polyp in group 2 with correlation coefficient (r) = 0. 1802. The probability that serum prolactin in diagnosis of endometrial cancer in group 2shows a positive test using serum prolactin = 71.42%. The probability that a endometrial cancer in group 2 shows a positive test using serum ca 125 = 57.14 %. There was a positive correlation between serum prolactin and serum ca-125 in the endometrial cancer in group 2 with correlation coefficient (r) = 0.118832. There was a negative correlation between serum prolactin and endometrial thickness in the endometrial cancer in group2 with correlation coefficient (r) = -0. 53533. There was a positive correlation between endometrial thickness and serum ca 125 in the endometrial cancer in group 2 with correlation coefficient (r) = 0. 272364.

Conclusion

The level of prolactin varies according to the type of AUB. Majority of the participants had prolactin level within the normal range. Around 25% of the participants had prolactin level above normal level in perimenpausal patients and 16%of postmenpausal patients. Thick endometrium is suspicious even if the female is not complaining of postmenopausal bleeding. Serum Prolactin levels are elevated in women suffering from endometrial cancers, making it a strong biomarker for these cancers. Study of endometrial histopathology in perimenopausal and postmenopausal women with abnormal uterine bleeding is helpful to diagnose hyperplasia and carcinoma of endometrium. Endometrial biopsy has for many years been the methods of choice for the diagnosis of endometrial cancer in patients with peri and postmenopausal bleeding. Apart from it, it reveals various endometrial patterns from proliferative, secretory, simple and complex hyperplasia with/without atypia, disordered proliferation and atrophic endometrium.

Recommendations

The presence of perimenopausal and postmenopausal abnormal uterine bleeding must be seriously and rapidly considered especially in overweight females having hypertension or diabetes mellitus years even uterine size is normal. All cases with thick endometrium especially if focal should have D & C biopsy. Trans-vaginal ultrasound should be done for any suspious endometrium in either pre or post menopause women. Serum prolactin may be used as a tumor marker for early detection of endometrial carcinoma.

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