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Essentiality of Understanding Complexities of Endometrial Hyperplasia

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Abstract

Background: Endometrial hyperplasia (EH), is categorized into EH without atypia, with atypia. EH carries risk of concomitant endometrial cancer (EC) potential for development of EC in future.

Objective: Study was conducted to know about cases of complex EH (CEH) with or without atypia, especially in context of body mass index (BMI), hypertension, and diabetes.

Methodology: Study was conducted at rural tertiary care centre. Only inpatient cases of histopathologically proved EH, CEH with atypia, CEHA, without atypia CEH over 9 years were included.

Results, Comments, Conclusion: There were 33cases of EH, 29 of CEHA, 4 only CEH. Twenty six (78.7%) patients were premenopausal, 7 (21.3%) postmenopausal. Seven women were around 40 years, 18 (54.5%) 40-49 years, 7(21.2%) of 50-59 years, (CEH) one (3%) 63yrs old, youngest 26 years old. Mean age of CEHA was 44.17 ± 6.4 years, CEH 41.5 ± 9.1 years. Mean parity of EH patients was 2.63, with CEHA 2.63 and for CEH 2.5. Only 2 (6.1%) women had never been pregnant, 2 (6.1%) had one birth, most women 87.87% had many births. Of 7 postmenopausal women who had CEH-A, two (33%) were postmenopausal for 6-10 years. Almost all women 27 (81.8%) had presented with abnormal uterine bleeding (AUB), only compliant, (23 CEH-A and 4 CEH). One had lower abdominal pain (CEH –A) as leading complaint. Fifteen (45.4%) women with CEHA were obese. BMI for CEH cases was 25.9 ± 3.3 kg/m2 for CEHA 29.2 ± 3.5 2, insignificant difference. Two (6.06%) women had hypertension (one CEH-A, one CEH), 2 (6.06%) patients had diabetes (both CEH-A), 2 (6.06 %) diabetes and hypertension (CEH-A). Of 33 patients, 25 (75.7%) underwent abdominal hysterectomy with bilateral salpingo- oophorectomy (TAH+BSQ,) 2 (6.06%), vaginal hysterectomy, 2 (6.06%) received progesterone therapy, 4 (12.12%) were lost. Of 7 women of 50-59 years, 6 with CEH-A, 5 had TAH + BSO, one did not take any therapy, one of CEH had TAH+ BSO, one 63 years, with CEH-A had TAH + BSO. For prevention of EC it is essential to keep high vigil for symptoms signs, provide appropriate treatment.

Keywords: Endometrial Hyperplasia; Body Mass Index; Lower Abdominal Pain; Histopathological Complexity; Postmenopausal; Endometrium; Progesterone Therapy

Abbreviations: EH: Endometrial Hyperplasia; EC: Endometrial Cancer; BMI: Body Mass Index; CEH: Complex Endometrial Hyperplasia; HIS: Hospital Information System; AUB: Abnormal Uterine Bleeding; EIN: Endometrial

Intraepithelial Neoplasia; IUD: Intra Uterine Devices; MA: Megestrol Acetate; MPA: Medroxyprogesteron Acetate.

Introduction

Endometrial hyperplasia (EH), proliferation of endometrial glands is categorized into EH without atypia and with atypia, referred to as endometrial intraepithelial neoplasia (EIN) in modern days [1]. EH is a common histopathological finding and usually results from unopposed estrogenic stimulation of the endometrium caused by exogenous or endogenous estrogen with a relative lack of the counter balancing effects of progesterone. It involves varying degrees of histopathological complexity and atypical features in the cells and nuclei. For prevention of the development of EC, it is essential that clinicians keep a high vigil for the symptoms and signs of EH which is a disordered proliferation of endometrial glands. EH is a condition in which the endometrium is abnormally thick. Earlier four types of EH used to be described on the basis of abnormal cells and the presence of cell changes. Simple, Complex, Simple atypical, Complex atypical hyperplasia [2]. However EH division has been simplified EH is caused by too much estrogen and/or not enough progesterone. EH carries risk of concomitant EC as well as the potential to progress to EC in future which is one of the commonest gynecological malignancies [3]. However despite a long history of disease and great efforts in research, practical and accurate system to differentiate true precancerous hyperplasia seems to be still evasive. Abnormal uterine bleeding (AUB) is reported to be the most common presenting symptom of EH [4-6]. Adult, premenopausal, post menopousal women invariably present with vaginal bleeding. Through postmenopausal women with atrophy of endometrium usually present with frequent, slight bleeding, spotting. Still EC must be considered [7] (Table 1).

Age	P0		P1- P2		P3-P4		≥ P5		Total	% of total
	N	%	N	%	N	%	N	%		
<40 years 7	2	28.57	3	42.85	2	28.57	0	0	7	100
Total	**2**	**28.57**	**3**	**42.85**	**2**	**28.57**	**0**	**0**	**7**	**100**
40-49 years 18	0	0	5	42.85	9	52.38	1	4.76	15	100
Total	**0**	**0**	**5**	**42.85**	**9**	**52.38**	**1**	**4.76**	**15**	**100**
50-59 years 7	0	0	4	40	6	60	0	0	10	100
Total	**0**	**0**	**4**	**40**	**6**	**60**	**0**	**0**	**10**	**100**
>60 years 1	0	0	0	0	1	100	0	0	1	100
Total	**0**	0	**0**	0	**1**	100	**0**	0	**1**	**100**
total	**2**	**6.6**	**12**	**36.36**	**18**	**54**	**1**	**3.3**	**33**	**100**

Table 1: Age and Parity of Women with Endometrial Hyperplasia with or without Atypia.

Objective

Study was conducted to know about cases of only complex EH (CEH) with or without atypia especially in context of body mass index (BMI) and hypertension, and diabetes.

Material and Methods

Study was conducted at a rural tertiary care centre with only inpatient cases of histopathologically proved EH, CEHA, without atypia CEH over a period of 9 years. Hospital information system (HIS) was used for information regarding demographic profile, detailed history, clinical examination, investigations, and management of retrospective cases with Estrogen-progeterone receptor status from patients' records and rechecking as per the study needs. Approval of the institute's ethics committee was taken and information was collected from all prospective patients after informed consent. For retrospective patients blanket consent that records could be used for research without identifying of patient was always taken. Inclusive criteria were histologically proved new cases of CEHA and CEH. Study records of all retrospective cases were retrieved and re reporting was done as per the classification used in the study and the slides of both retrospective and prospective cases were reviewed to have uniformity. Limitations of study were cases, only inpatient cases of CEH were included with retrospective and prospective cases with possibilities of under inclusion.

Study Design

It was cross sectional hospital based, retrospective and prospective exploratory study of cases of 9 years, 7 years retrospective and 2 years prospective. So no sample size calculation was used.

Results

There were 33cases of EH, 29 cases of CEHA and 4 only CEH. Twenty- six (78.7%) patients were premenopausal and 7(21.3%) post-menopausal. Seven women were around 40 years, 18 (54.5%) 40-49 years, 7(21.2%) of 50-59 years and only one (3%) of 63yrs. Of the women who had CEH, the youngest was 26 years old. The mean age of the patients of CEHA was 44.17 ± 6.4 years and CEH 41.5 ± 9.1 years, of all cases none had age of menarche (AOM) below 12years, one (3%) AOM 12 years, 24 (72.7%) 13 years, [8] (24.2%) 14 years, AOM was 13.8+ 0.4 years, 13.5+0.5 years for CEH and 13.1+0.3 years for CEH-A, little less for CEHA (P value 0.0001). The mean parity of patients with CEHA was 2.63 (SD ±1.16) and for CEH 2.5 (SD±1.3) Two (6.1%) women had never been pregnant, 2 (6.1%) had one birth, 11 (33.3%) 2 births, 10(30.3%) 3 births, 7 (21.2%) 4 births and one had 5 births (p- value was 0.035) and most women (87.87%) had many births. One (3.03%) woman with CEH-A had last child birth (LCB) between 0-5 years, 3 (9.09%) between 6-10 years, (CEH-A), 6 (18.18%) between 11-15 years (CEH-A), 11 (33.33%) between 16-20 years (8 CEH-A and 3 CEH), 7 (21.21%) between 21-25 years (CEH-A), 2 (6.06%) between 26-30 years (CEH-A) and one (22.58%) more than 30 years (CEH-A) (Table 2).

Last birth	Menstrual Status	Menstrual Complaints		Lower Abdominal Pain		Others Including Vaginal Discharge as Leading		N	%
No birth	Menstruaring	2	100	0	0	0	0	2	100
	Total	2	100	0	0	0	0	2	100
1-19 years									
Menstruaring	12	92.3	1	7.69	0	0	13	100	
	Post Menopasual	2	7.14	2	33.33	0	0	4	100
	Total	14	82.35	3	17.64	0	0	17	100
>20-29 years									
Menstruaring	8	87.5		0	0	0	8	100	
	Post Menopasual	5	25	1	25	2	50	4	100
	Total	8	66.66	1	8.33	0	0	12	100
Total		27	81.81	4	12.12	2	6.06	33	100

Table 2: Last child birth, menstrual status and complaints.

Of 7 postmenopausal women who had CEH-A, two (33%) were postmenopausal for 6-10 years (one of 50- 59 years and one between 60-65 years, and five (71%) had menopause between 0-5 years, 2 of 40 -49 years, 3 of 50-59 years. Almost all women had presented with perimenopausal or postmenopausal bleeding as the leading complaint. Over all 27 (81.8%) women presented with bleeding as the only compliant (23 CEH-A and 4 CEH), One had lower abdominal pain (CEH –A) as leading complaint, 4 (12.1%) had lower abdominal pain (all CEH-A), one (3.03 %) had vaginal discharge (CEH-A) and one (3.03%) vulval swelling (CEH-A) also. Fifteen (45.4%) women with CEHA were obese. BMI for CEH cases was 25.9 ± 3.3 kg/m^2 and for CEHA cases was 29.2 ± 3.5 2, insignificant difference (p-value-0.07). Two (6.06%) women had hypertension (one CEH-A and one CEH), 2 (6.06%) patients had Diabetes (both CEH-A), two (6.06 %) women had Diabetes as well as hypertension (CEH-A), one (3.03%) was treated case of breast Cancer (CEH-A) and 2 women (6.06%) had Polycystic ovarian syndrome (PCOS) (CEH-A) also (Table 3).

Age in 6 (years	Age of menarche	Complex endometrial hyperplasia with atypia		Complex endometrial hyperplasia		No	%
		no	%	no	%		
<40 years	11/12 years	1	14.28	0	0	1	14.28
7	13/14years	5	71.42	1	14.28	6	85.71
	TOTAL	6	85.71	1	14.28	7	100
40-49 years	13/14 years	16	88.88	2	11.11	18	100
18	TOTAL	16	88.88	2	11.11	18	100
50-59 years	13/14 years	6	85.71	1	14.28	7	100
7	TOTAL	6	85.71	1	14.28	7	100
>60years							
1	13/14 years	1	100	0	0	1	100
	TOTAL	1	100	0	0	1	100
TOTAL		29	87.87	4	10.52	33	100

Table 3: Age, Age of Menarche and CEH.

The total 33 patients, 25 (75.7%) underwent abdominal hysterectomy with bilateral salpingo- oophorectomy (TAH+BSQ), 2 (6.06%) vaginal hysterectomy, 2 (6.06%) received progesterone therapy and 4 (12.12%) were lost. Of the 7 patients of less than 40 years, 6 were with CEH-A, 4 had TAH + BSO, one progesterone therapy and one did not receive any therapy as was lost to follow up. One woman with CEH received progesterone therapy. Of the 18 patients of 40-49 years, 16 were cases of CEH-A and 12 had TAH+BSO, 2 had vaginal hysterectomy and 2 did not receive any treatment. Two patients of CEH of this age had TAH + BSO.

Of the 7 women of 50-59 years, 6 were with CEH-A, 5 had TAH + BSO and one did not take any therapy and one of CEH had TAH+ BSO. One woman who was 63 years, with CEH-A had TAH+BSO.

Discussion

Many researchers [8-11] and others opined that EH, if not treated, has the propensity to develop into EC. EH is believed to be because of chronic exposure to estrogen along with a relative deficiency of progesterone. The risk factors include later age, nulliparity, obesity, PCOS, anovulatory cycles, genetic, diabetes mellitus, hypertension [9,10]. Siegel [11,12] opined that if CEH, specially, CEHA was caught early prevention of progression to EC was possible. A large study conducted about the epidemiology of CEH revealed that women who had EH without atypia were usually between the age of 50-54 years. EH with atypia has been most commonly reported between 60-64 years, and quite rare below the age of 30 years [13]. Far and Baker [14] reported age for CEH cases around 40-49 years, women younger. In the present study, though only cases of CEH with or without atypia were included, still patients were younger, one who had CEH was only 26th years and 7 cases were around 40 years, 18 (54.5%) 40-49 years as reported by some other authors also [14]. No one was above 65 years. The mean age of the patients of CEH-A was 44.17 ± 6.4 years, and that for CEH was 41.5 ± 9.1 years. P value (0.00001). In the present study the mean parity of CEH patients was 3(SD+1.61), 82.53% patients had 2 or more births. Ricci, et al. [15] reported increase in CEH incidence with increase in parity. Research also revealed increase in CEH incidence with increase in parity, though EH was reported to be more common in women who never had pregnancy but was not uncommon in women with many births also. Other researchers have also studied it's association, however did not find any significance [16]. In the present study of 33 patients 26 cases were pre-menopausal and only 7 (21.1%) postmenopausal, most women with many births, only two had never been pregnant. Almost all women had presented with AUB, perimenopausal as well as postmenopausal as the leading complaint. Only one had lower abdominal pain (CEH –A) as leading complaint. Over all 27 (81.8%) women presented with bleeding as the only compliant (23 CEH-A and 4 CEH), 4 (12.1%) had lower abdominal pain (all CEH-A), as main complaint , one (3.03 %) vaginal discharge (CEH-A) and one (3.03%) vulval swelling (CEH-A) also. However CEH cases were only 4. Earlier division of EH was complicated. WHO simplified the classification of EH and proposed only two categories based upon the presence of cytologic atypia , CEH and CEHA [17]. This classification was followed in the present study also. In

the study of Ellenson [7] 226 women who presented with postmenopausal bleeding, 7% were found to have EC, 56% had atrophy and 15% were diagnosed with some form of EH. A study compared hypertensive and nonhypertensive women and found that 20% of postmenopausal women who had hypertension had increased endometrial thickness [18]. Study by Gredmark [19] revealed that postmenopausal women with adenomatous and atypical hyperplasia of the endometrium had linkage to severe obesity (BMI of 30 or over), which implied long – term exposure to endogenous estrogen and data of menopausal status revealed a marked increase in risk of postmenopausal women. Fifteen (45.4 %) patients of CEH-A were obese. BMI for CEH-A was 25.9 ± 3.3 kg/m2 and CEH was 29.2 ± 3.5 kg/m2, difference insignificant (p-value- 0.07). Only 2 (6.06%) women had hypertension (one CEH-A and one CEH), 2 (6.06%) patients had Diabetes (both CEH-A), 2 (6.06%) had PCOS (both CEH-A) and 2 (6.06 %) women had Diabetes with hypertension (CEH-A). Present study did not find a substantial relation between CEH-A and hypertension and diabetes, consistent with others findings[20] but with small numbers also some had hypertension, diabetes or both.

It is known that EH devoid of atypia are not cancer precursors, EH with cytoligic atypia may progress to EC. In a prospective study with a mean follow- up of 7 years, none of the 65 women with EH , without atypia developed EC, but but 5 to 20 EH with atypia had EIN, a lesion that is likely to regress, persist, or progress to invasion [1]. Nappi et.al [21] reported that CEH was considered a heterogeneous pre-neoplastic clinical entity characterized by an abnormal glandular proliferation, with less than half of the tissue area occupied by the stroma. Ronnett [22] reported that glandular proliferation with significant nuclear atyapia is EC precursors. The figure most often cited for progression of adenomatous hyperplasia with atypia to EC has been 30% at 10 years [23]. Ricci et al [15] opined that cystic hyperplasia, adenomatous hyperplasia and anaplasia were capable of spontaneous regression. In the present study only complex hyperplasia cases as per WHO classification (2014) were included [24]. Prip, et al. [25] reported strong association between CEHA, with EC in 2.9% cases and among women who remained at risk for more than 3 months after initial diagnosis of non-atypical EH progression to CEHA or EC was seen in 13%. Sixty-six percent of the women with progressive disease were diagnosed with CEHA or EC more than one year after initial diagnosis, but only two were diagnosed later than 5 years. The universal standard procedure for diagnosis of intrauterine disorders is dilatation and curettage (D&C) but some investigators have reported that D&C lacks accuracy and reliability compared with other diagnostic methods [26]. And in around 60% of the D&C procedures, less than half of the uterine cavity is curetted, thereby questioning the accuracy of this method [27]. However in the present study this was the main diagnostic mode with well correlation, even after hysterectomy. EH is treated either conservatively or surgically depending on the histopathological type, the age of patient, fertility needs and the presence of other risk factors. The most common treatment is progestin. This can be taken in several forms, including pill, injection, vaginal cream, or intrauterine device with hormones (IUD). The main purpose of therapy is prevention of EC, more often for controlling bleeding. Jarvela and Santala [28] reported that thermal ballon endometrial ablation therapy was effective as traditional progesterone administration in the treatment of non-atypica EH, however the hysterectomy rate during the follow-up period was considerably high, and, therefore, hysterectomy might be considered even a first choice treatment for EH in those depending on age and need of future fertility. Mutter [29] opined that the high cancer risk conferred by an EIN diagnosis included a 36% incidence of occult carcinoma, one third, even myoinvasive. This must be carefully considered in deciding upon appropriate therapy. Lee [30] reported that oral progestins were associated with poor compliance and systemic side effects that may limit overall efficacy. Although some cases of EIN/ early intramucosal adenocarcinoma respond to exogenous progestagens, ovulation inducers, or both, in most cases the lesions tend to recur within few months to few years after delivery of the new-born if hormonal management is for preserving fertility.

Oral progestin, megestrol acetate (MA) and medroxyprogesteron acetate (MPA) are the most commonly used methods with various regimens available for treatment of EH [31]. In the present study numbers were small and only 6% received this treatment. Of the 7 patients of around 40 years, 6 had CEH-A 4 had TAH + BSO, on progesterone therapy and one was lost to follow up and one with CEH received progesterone therapy. Of the 18 patients of 40-49 years, 16 were cases of CEH-A, 12 had TAH + BSO, 2 vaginal hysterectomy and 2 were lost two patients with CEH had TAH + BSO. Of the 7 women of 50-59 years, 6 with CEH-A, 5 had TAH + BSO, one with CEH had TAH+ BSO. TAH and BSO is recommended in cases of CEHA in symptomatic women with AUB and women in the post reproductive age [32]. Surgery is justified because of 25-35% progression rates to invasion if EC and 80% failure rate to respond to progestational therapy. Women who have CEH A because of estrogen alone replacement, benefit from the addition of progestin into their replacement regimen [9]. Barr, et al. [33] did a study and reported Serum HE4 predicts progestin treatment response. Baseline serum HE4 was significantly higher in non-responders. Older age baseline serum HE4 and endometrial histology were associated with a lower likelihood of progestin treatment response. Such things are neither available nor affordable for women with low resources. Spontaneous resolution can occur if the hormonal

milieu is corrected. Both intrauterine (levonorgestrel-releasing intrauterine system [LNG-IUS]) and continuous oral progestogens can be used for the treatment. Over all of the 33 patients, 25 (75.7%) women had TAH+BSO, 2 (6.06%) had vaginal hysterectomy, 2 (6.06%) received progesterone therapy and 4 (12.12%) were lost. For prevention of EC it is essential to keep a high vigil for the signs and symptoms of EH and provide appropriate treatment.

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