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STUDY OF IMMUNOHISTOCHEMICAL EXPRESSION OF BETA-CATENIN IN ENDOMETRIAL BIOPSY SPECIMENS AMONG PATIENTS OF ABNORMAL UTERINE BLEEDING IN A TERTIARY CARE HOSPITAL

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ABSTRACT **Context** The primary role of endometrial sampling in patients with AUB is to determine whether carcinoma or premalignant lesions are present by evaluating histologically. β-catenin has been one among the important markers studied to differentiate between benign EH and premalignant EIN. **Aims:** 1) To analyse the expression of β-catenin in various endometrial lesions 2) To define the diagnostic accuracy of β-catenin in differentiating benign EH from premalignant EAH/EIN. **Settings and Design:** Prospective study conducted at Department of Pathology in a tertiary care hospital over a period of two years. **Methods and Materials:** β-catenin immunoexpressions were evaluated using immunohistochemical staining in 150 histopathologically diagnosed cases of endometrial lesions from AUB cases. Statistical analysis used: The statistical analysis was done using Pearson's Chi-squared test. **Results:** This study included Proliferative endometrium (22 cases), Benign endometrial hyperplasia (57 cases), Endometrial atypical hyperplasia/ Endometrioid intraepithelial neoplasia (56 cases) and Endometrioid carcinoma (15 cases). 50% cases of PE showed β-catenin membranous expression, 56% cases of BEH showed cytoplasmic expression, 27% cases of EAH/EIN and 60% of EMC showed nuclear expression. Statistically significant association was seen between the location of β-catenin expression and different endometrial lesions ($p<0.001$). Diagnostic accuracy in differentiating benign EH from premalignant EAH/EIN was high with considering only nuclear β-catenin as aberrant expression and was low by considering cytoplasmic and /or nuclear β-catenin as aberrant expression. **Conclusion** Nuclear expression of β-catenin strongly correlates with increasing grades of endometrial pathology, namely endometrial atypical hyperplasia/ endometrioid intraepithelial neoplasia and endometrioid carcinoma. Also nuclear expression of β-catenin appears as a little sensitive, but perfectly specific marker of endometrial precancer (EAH/EIN).

KEYWORDS : Beta catenin, Diagnostic accuracy, Endometrial hyperplasia, Endometrioid intraepithelial neoplasia, Nuclear expression

INTRODUCTION

Abnormal uterine bleeding (AUB) is the most common menstrual problem in women of all ages consulting a Gynecologist.[1] Early diagnosis and timely treatment of AUB is necessary to rule out malignancy. Endometrial curettage is the most commonly used method for evaluation of AUB.[2] Endometrial curettage followed by histopathological examination can be used for definitive diagnosis of AUB.

Endometrial hyperplasia is one of the most frequent causes of AUB. In 10% of premenopausal women with AUB, histological findings show endometrial hyperplasia and in 6% of postmenopausal women with uterine bleeding, endometrial cancer is found.[3] Endometrial cancer is the fifth leading cancer among women worldwide which accounts for 4.8% of all cancers in women.[4]

Beta-catenin, a cadherin associated protein is encoded by CTNNB1 gene and is a key protein in the Wnt signalling pathway, that has a dual role in cell adhesion and transcriptional activation. Beta-catenin is a proto -oncogene. While Wnt - β-catenin pathway plays a physiological role in embryo development and cell proliferation, its pathologic activation can lead to cancerous transformation.[5],[6],[7] So in this respect, Wnt - β-catenin pathway is known to be involved in endometrial carcinogenesis with specific reference to endometrioid carcinoma and its precursor.[6],[7],[8]

The aim of this study was to analyse the expression of β-catenin in proliferative (normal) endometrium (PE), benign hyperplasia (BEH), endometrial atypical hyperplasia/ endometrioid intraepithelial neoplasia (EAH/EIN) and endometrioid carcinoma (EMC) and to define the diagnostic accuracy of β-catenin in differentiating benign EH from premalignant EAH/ EIN, assessing how the accuracy is influenced by the criteria used to define β-catenin pattern as aberrant (i.e., only nuclear or Cytoplasmic / nuclear).

MATERIALS AND METHODS

This was a prospective study conducted at Department of Pathology in a tertiary care hospital over a period of two years.

A total of 150 histopathologically diagnosed cases of endometrial lesions [BEH, AH/EIN and EMC) including Proliferative (normal) endometrium (PE)] from abnormal uterine bleeding cases were included in this study. Endometrial sampling was obtained by Dilatation & Curettage. The biopsy specimens were fixed in 10% neutral buffered formalin and completely submitted for tissue processing and paraffin wax embedding. Two micro sections of 4-5 micron thickness were prepared from the corresponding paraffin blocks, one on albumin coated slide for H&E staining and the other on poly L- lysine coated slide for immuno histochemical staining.

Appropriate positive and negative controls are used for the antibody. Colon tissue positive for β – catenin is taken as control for the assessment. The primary antibody is omitted in the negative controls.

For evaluation of β-catenin immunoreactivity, brown granules staining reaction in the cells was considered positive and loss of staining was considered negative. The following parameters were assessed : location of β-catenin, and the intensity of β – catenin expression.[9]

If only membranous was stained it was considered as membranous positive. If both the membrane and cytoplasm were stained it was considered as cytoplasmic positive. If both the cytoplasm and nucleus were stained it was considered as nuclear positive. Cytoplasmic and membranous staining assessed in 4 grades. A scale 0 to 3 was used to grade the expression. A IHC score of 0 was considered as no expression; IHC score of 1+, 2+ and 3+ were considered as weak, moderate and strong expression, respectively. Nuclear staining was assessed as positive or negative expression. During statistical evaluation cytoplasmic and membranous group indicating weak expression (1+) was included into 'no expression' group.[10]

Diagnostic accuracy of β-catenin expression in differentiating between benign and premalignant EH was evaluated.
β-catenin expression was the index test, while EH morphology was the reference standard.EH specimens with β-catenin nuclear expression was considered as 'true positive' when they showed premalignant EAH /EIN morphology, and 'false positive' when they showed benign EH morphology. On the other hand, EH without β-catenin nuclear expression was considered as 'true negative' when they showed Benign EH morphology and 'false negative' when they showed premalignant EAH /EIN morphology.

Diagnostic accuracy was assessed as sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic OR (DOR). DOR was used to quantity the overall diagnostic accuracy, as follows:
DOR ≤ 1: no accuracy
1 < DOR < 3: very low accuracy
3 ≤ DOR < 10: low accuracy
10 ≤ DOR < 25: moderate accuracy
25 ≤ DOR < 100: high accuracy
DOR ≥ 100: very high accuracy.[11]

Statistical Analysis
The statistical analysis was done for all the data using Pearson's Chi-squared test. The results were considered statistically significant if the p value was <0.05.

RESULTS
A total of 150 cases were included in the present study. 22 cases (14.7%) was proliferative endometrium (PE), 57 cases (38%) was benign endometrial hyperplasia (BEH), 56 cases (37.3%) was endometrial atypical hyperplasia/ endometrioid intraepithelial neoplasia (EAH /EIN) and 15 cases (10%) was endometrioid carcinoma (EMC).Age of the patients ranged from 30 to 70 years. 28 cases (49.1%) of benign hyperplasia and 17 cases (77.3%) of proliferative endometrium were 30-40 years of age and 26 cases (46.4%) of EAH /EIN were seen in 5th decade of life. 7 cases (46.7%) of endometrioid carcinoma were seen in 6th decade of life.Out of 150 cases, 91% of the cases were multiparous, while only 9% of the cases were nulliparous. Out of all cases, 90% cases of BEH and 77% cases of EAH /EIN were pre-menopausal while 87% cases of EMC were post-menopausal.The localization of β-catenin in different endometrial lesions are shown in Table 1.

TABLE 1: Localization of β-catenin in different endometrial lesions (n=150)

Location of β-catenin	PE [n=22 (100%)]	BEH [n=57 (100%)]	EAH/EIN [n=56 (100%)]	EMC [n=15 (100%)]	x2	p value
Membranous	11 (50%)	25 (44%)	9 (16%)	1 (7%)	26	<0.001 (S)
Cytoplasmic	11 (50%)	32 (56%)	32 (57%)	5 (33%)	29.7	<0.001 (S)
Nuclear	0 (0%)	0 (0%)	15 (27%)	9 (60%)	27	<0.001 (S)

*The results are significant at p value <0.05.
† PE– Proliferative endometrium, BEH- Benign endometrial hyperplasia
‡ EAH/EIN– Endometrial atypical hyperplasia/ endometrioid intraepithelial neoplasia
§ EMC– Endometrioid carcinoma. **Source: Original**

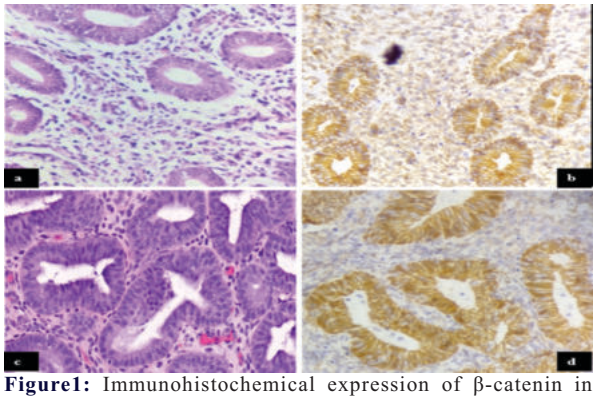

Figure1: Immunohistochemical expression of β-catenin in Proliferative endometrium and Benign endometrial hyperplasia. (a) Histopathological image of Proliferative endometrium (H&E, x40). (b) Moderate membranous expression in Proliferative endometrium (IHC, x40). (c) Histopathological image of Benign endometrial hyperplasia (H&E, x40). (d) Moderate cytoplasmic expression in Benign endometrial hyperplasia (IHC, x40**). Source: Original**

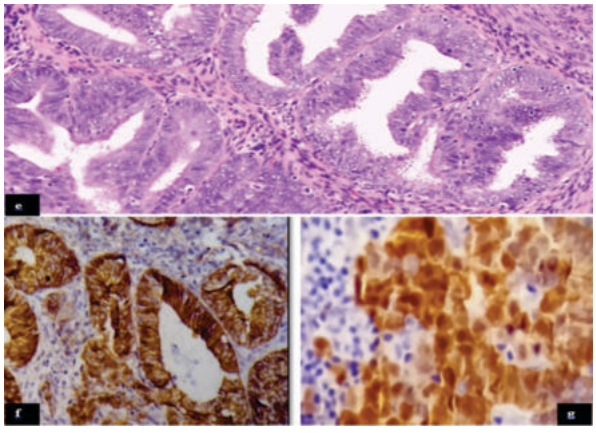

Figure 2: Immunohistochemical expression of β-catenin in endometrial atypical hyperplasia (EAH/EIN). (e) Histopathological image of endometrial atypical hyperplasia (H&E, x40). (f) Strong cytoplasmic expression in endometrial atypical hyperplasia (IHC, x40). (g) Nuclear expression in endometrial atypical hyperplasia (IHC, x40). **Source: Original**

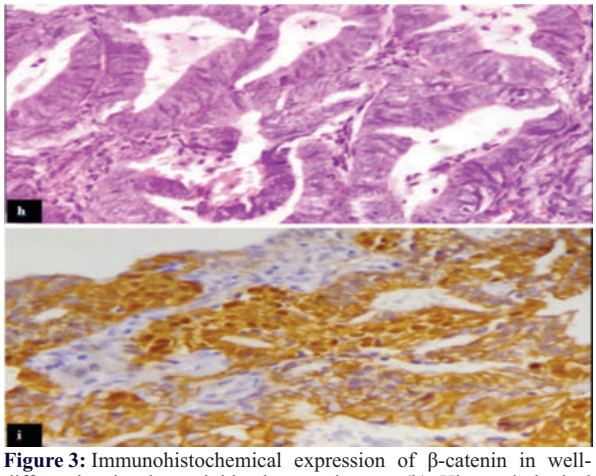

Figure 3: Immunohistochemical expression of β-catenin in well-differentiated endometrioid adenocarcinoma. (h) Histopathological image of well-differentiated endometrioid adenocarcinoma (H&E, x40). (i) Nuclear and strong cytoplasmic expression in well-differentiated endometrioid adenocarcinoma (IHC, x40). **Source: Original**

The intensity of membranous β-catenin expression in different endometrial lesions are shown in Table 2.

TABLE 2: Intensity of Membranous β-catenin expression in endometrial lesions in the present study

Intensity (IHC Score)	PE [n=11 (100%)]	BEH [n=25 (100%)]	EAH/EIN [n=9 (100%)]	EMC [n=1 (100%)]
0/ 1+	00 case (0%)	07 cases (28%)	03 cases (33.3%)	01 case (100%)
2+	11 case (100%)	10 cases (40%)	05 cases (55.6%)	00 case (0%)
3+	00 case (0%)	08 cases (32%)	01 case (11.1%)	00 case (0%)

*The chi-square statistic is 15.66533. p value is 0.0156. The result is significant at p value <0.05.
† PE – Proliferative endometrium, BEH- Benign endometrial hyperplasia
‡ EAH/EIN – Endometrial atypical hyperplasia/ endometrioid

intraepithelial neoplasia
§ EMC – Endometrioid carcinoma.

Source: Original

The intensity of cytoplasmic β-catenin expression in different endometrial lesions are shown in Table 3.

TABLE 3: Intensity of Cytoplasmic β-catenin expression in different endometrial lesions

Intensity (IHC Score)	PE [n=11 (100%)]	BEH [n=32 (100%)]	EAH/EIN [n=32 (100%)]	EMC [n=5 (100%)]
0/ 1+	08 cases (72.7%)	05 cases (15.6%)	02 cases (6.3%)	01 case /(20%)
2+	03 cases (27.3%)	15 cases (46.9%)	13 cases (40.6%)	01 case (20%)
3+	00 case (0%)	12 cases (37.5%)	17 cases (53.1%)	03 cases (60%)

*The chi-square statistic is 26.276988. p value is 0.0001976. The result is significant at p value <0.05.
† PE – Proliferative endometrium, BEH- Benign endometrial hyperplasia
‡ EAH/EIN – Endometrial atypical hyperplasia/ endometrioid intraepithelial neoplasia
§ EMC – Endometrioid carcinoma.

Source: Original

Fifteen (27%) cases of EAH / EIN and nine (60%) cases of EMC showed positive nuclear expression, respectively.

The sensitivity, specificity, positive and negative likelihood ratio, and Diagnostic accuracy of β-catenin immunoexpression in differentiating Benign EH from Premalignant EAH / EIN are shown in the Table 4 and Table 5, respectively.

TABLE 4: Statistic metrics of immunohistochemistry of β-catenin in differentiating BEH from Premalignant EAH/EIN

Nuclear expression only criterion			**Cytoplasmic and/or Nuclear expression criterion**		
Statistic	**Value**	**95% CI**	**Statistic**	**Value**	**95% CI**
Sensitivity	0.27	0.16 – 0.40	Sensitivity	0.84	0.72 – 0.92
Specificity	1	0.94 – 1	Specificity	0.44	0.31 – 0.58
LR +	----	----	LR +	1.49	1.16 – 1.93
LR -	0.73	0.62 – 0.86	LR -	0.37	0.19 - 0.71

*BEH- Benign endometrial hyperplasia
† EAH/EIN – Endometrial atypical hyperplasia/ endometrioid intraepithelial neoplasia

Source: Original

TABLE 5: Diagnostic accuracy of immunohistochemistry of β-catenin in differentiating BEH from Premalignant EAH/EIN

Nuclear expression only criterion		**Cytoplasmic and/or Nuclear expression criterion**	
DOR	42.9518	DOR	4.0799
95% CI	2.4986 to 738.3706	95% CI	1.6847 to 9.8802
z statistic	2.591	z statistic	3.116
p value	0.0096 (S)	p value	0.0018 (S)
Overall accuracy	High accuracy	Overall accuracy	Low accuracy

*The result is significant at p value <0.05.
†BEH- Benign endometrial hyperplasia
‡ EAH/EIN – Endometrial atypical hyperplasia/ endometrioid intraepithelial neoplasia

Source: Original

DISCUSSION

Endometrial hyperplasia is one of the most frequent causes of AUB, which leads to endometrial cancer if left untreated. Endometrial hyperplasia (EH) is a pathological condition characterised by irregular proliferation of endometrial glands with an associated increase in gland to stroma ratio when compared with proliferative endometrium. Most cases of endometrial hyperplasia result from high levels of estrogen, unopposed by progesterone. [12]

EIN is of clinical significance because it is often a precursor lesion of type I endometrioid carcinoma. [13] There is increased risk of coexisting (39% of women with EIN will be diagnosed with carcinoma within one year) or future endometrial carcinoma (long term cancer risk is 45 times greater for a woman with EIN compared to one with only a benign endometrial histology). EIN is a monoclonal premalignant endometrial gladular lesion that precedes the development of endometrioid- type endometrial adenocarcinoma. [14]

Endometrial cancers are classified into two broad types, type I and type II. Type I tumors encompasses about 80% to 85% of cases, are low grade, estrogen – related and consists of endometrioid carcinoma (EMC) and its histologic variants. Type II endometrial cancers are non - endometrioid, unrelated to estrogen stimulation and include serous carcinoma and clear cell carcinoma.

Different patterns of molecular alterations are seen in the pathogenesis of endometrial carcinomas. [15], [16] The common genetic alterations in EMC are microsatellite instability, PTEN mutation, Beta- Catenin, PIK3CA and KRAS. [17]

In the present study, 27% of atypical hyperplasia/ endometrioid intraepithelial neoplasia and 60% of endometrioid endometrial carcinoma showed nuclear localization of β-catenin. The difference in location of β- catenin expression and the intensity of β- catenin expression between PE, BEH, EAH/EIN and EMC was statistically significant, with presence of nuclear β- catenin expression in EAH/EIN and EMC (p<0.001). Thus findings in the present study were concordant with the findings of sarkar et al [9] who observed statistically significant association between nuclear positivity of β- catenin with increasing severity of endometrial pathology (p<0.001). 20% of atypical hyperplasia and 46% of endometrial carcinoma showed nuclear localization of β- catenin and they also noted statistically significant association between the intensity of β- catenin expression and the histological diagnosis (p<0.001).

Mariem El – Fiky et al [18] observed that cytoplasmic and nuclear β – catenin immunoexpression may be useful for a correct early diagnosis of endometrioid carcinoma with positive cytoplasmic expression in 52% cases of endometrioid carcinoma and positive nuclear expression in 48% cases of endometrioid carcinoma which was higher than in endometrial hyperplasia cases (48% vs 8%). In the present study, higher nuclear β – catenin expression was seen in endometrioid carcinoma (60%) than endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia (27%) and benign endometrial hyperplasia with no nuclear expression (0%). However, positive cytoplasmic expression was more in EAH/EIN (57%) than EMC (33%) in the present study.

In the present study, EAH/EIN and EMC showed significantly higher nuclear positivity (27% in EAH/EIN; 60% in EMC) and lower membrane positivity (16% in EAH/EIN; 7% in EMC) compared to PE (50% membrane positive) and BEH (44% membrane positive). These findings in the present study are concordant with the findings of Xiong Y et al [19] who observed that abnormal (marked membranous / cytoplasmic, cytoplasmic and / or nuclear) expression rates of β- catenin in EIN lesions (50%) and endometrioid adenocarcinoma (66.7%) were significantly higher than that of benign hyperplasia (10.2%) respectively (p<0.01).

Norimatsu Y et al [20] reclassified 117 cases in Japanese women that were initially diagnosed as endometrial hyperplasia according to WHO classification and compared them with the results of PTEN and β- catenin immunohistochemistry. Out of 38 reclassified EIN cases, nuclear β- catenin staining was seen in 26.3% of EIN cases and none of the BAC or NPE cases showed positive nuclear staining. They concluded that positive nuclear staining of β- catenin were frequently seen in EIN but were not seen in NPE or BAC cases. Similarly in the present study, 27% of EAH/EIN cases showed nuclear positivity and none of the PE and BEH cases showed nuclear expression of β- catenin. Thus the nuclear expression of β- catenin were statistically more frequent in EAH/EIN cases than PE and BEH in the present study.

Diagnostic accuracy of β- catenin in differentiating BEH from Premalignant EAH/EIN in the present study comparison with literature is shown in Table 6.

TABLE 6: Comparison of literature with present study: Diagnostic accuracy of β-catenin in differentiating BEH from Premalignant EAH/EIN

	Type of study & sample size	Subgroup analysis	Diagnostic accuracy of β-catenin expression	
Present study	Case study (systematic review) 150 specimens	Not done	Nuclear High accuracy	Cytoplasmic &/or nuclear Low accuracy
Antonio Travaglino et al	Meta analysis study (12 studies) 1510 specimens	WHO or EIN classification	Nuclear WHO – Very low accuracy EIN- Moderate Accuracy	Cytoplasmic &/or nuclear WHO- Absent EIN- Low accuracy

*BEH- Benign endometrial hyperplasia
† EAH/EIN – Endometrial atypical hyperplasia/ endometrioid intraepithelial neoplasia

Source: Original

In the present study, considering nuclear β- catenin aberrant expression, the diagnostic accuracy was high; while considering cytoplasmic and / or nuclear expression, the diagnostic accuracy was low. 27% cases of premalignant EAH/EIN showed nuclear β- catenin positivity while none of the benign EH cases showed nuclear β- catenin expression. Thus these findings support that nuclear β- catenin is a marker of premalignancy with high diagnostic accuracy and perfect specificity but with a low sensitivity. However, there was significant increase in nuclear β-catenin expression from EAH/EIN to EMC (27% vs 60%, respectively).

These findings in the present study are compared with Antonio Travaglino et al. [11]. But the variation in results is due to differences in the study design, sample size and the subgroup classification system adopted in the given study.

CONCLUSION

Normal β-catenin expression in endometrial glandular cells during proliferative phase is on membrane and in cytoplasm. In the present study, it was reinforced that nuclear expression of β-catenin strongly correlates with increasing grades of endometrial pathology, namely endometrial atypical hyperplasia / endometrioid intraepithelial neoplasia and endometrioid carcinoma. Also nuclear expression of β-catenin appears as a little sensitive, but perfectly specific marker of endometrial precancer (EAH/EIN). Since low sensitivity makes β-catenin IHC inadequate as a stand-alone diagnostic test, β- catenin can be used as a highly reliable rule-in test for diagnosing endometrial precancer. As hysterectomy is the standard treatment for premalignant EAH/EIN, a highly specific test may avoid the risk of severe overtreatment. Thus β-catenin can be used as a surrogate marker in early diagnosis of premalignant lesion (EAH/EIN) and also as a prognostic marker in patients with endometrioid carcinoma.

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