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Immunohistochemical Evaluation of Bcl-2 and Ki-67 Expression in Cyclical Endometrium, Endometrial Hyperplasia, And Endometrial Carcinoma

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KEYWORDS

Endometrial carcinoma; Endometrial hyperplasia; Bcl-2; Ki-67; Immunohistochemistry; Cell proliferation; Apoptosis

ABSTRACT:

Background: Endometrial carcinoma is the most common malignancy of the female genital tract and is often preceded by precursor lesions such as endometrial hyperplasia. Molecular markers that regulate apoptosis and cell proliferation may play an important role in the progression from hyperplasia to carcinoma. Bcl-2 is an anti-apoptotic protein that prolongs cell survival, while Ki-67 is a nuclear proliferation marker associated with cellular growth.

Aim: To evaluate the immunohistochemical expression of Bcl-2 and Ki-67 in normal cyclical endometrium, endometrial hyperplasia, and endometrial carcinoma, and to determine their role in endometrial tumorigenesis.

Materials and Methods: This descriptive study (retrospective and prospective) was conducted in the Department of Pathology, Meenakshi Medical College Hospital and Research Institute, Tamil Nadu, from January 2014 to April 2017. A total of 60 endometrial tissue specimens were analyzed, including proliferative endometrium (n=10), secretory endometrium (n=10), endometrial hyperplasia (n=25), and endometrial carcinoma (n=15). Immunohistochemistry for Bcl-2 and Ki-67 was performed using the avidin–biotin complex method. The proportion and intensity of staining were evaluated and statistically analyzed.

Results: Bcl-2 expression was positive in 73% of cases overall, with 100% positivity in proliferative endometrium, 40% in secretory endometrium, 76% in endometrial hyperplasia, and 73% in endometrial carcinoma. Strong Bcl-2 expression was observed mainly in hyperplasia and low-grade carcinoma. Ki-67 expression was positive in 70% of cases, with higher expression in hyperplasia (76%) and carcinoma (80%). Strong Ki-67 positivity was predominantly seen in complex hyperplasia with atypia and poorly differentiated carcinoma, indicating increased proliferative activity.

Conclusion: Bcl-2 expression increases during the progression from simple hyperplasia to atypical hyperplasia and is more prominent in low-grade carcinoma, suggesting its role in early tumorigenesis. In contrast, Ki-67 expression correlates with lesion severity and tumor grade, reflecting increased proliferative activity in advanced lesions. These findings indicate that Bcl-2 and Ki-67 may serve as useful diagnostic and prognostic markers in the progression of endometrial hyperplasia to carcinoma.

INTRODUCTION

Endometrial carcinoma is the most common malignancy of the female genital tract, with endometrioid carcinoma (Type I) being the most frequent subtype. It is often preceded by identifiable precursor lesions collectively termed endometrial hyperplasia, making early detection clinically important for cancer prevention and timely management. Globally, endometrial cancer affected approximately 320,000 women and caused about 76,000 deaths in 2012. Although the exact etiology remains unclear, several risk factors have been identified, including nulliparity, early menarche, late menopause, obesity, diabetes mellitus, hypertension, high body mass index, and family history of endometrial cancer. [1, 2] Unopposed estrogen exposure is considered a major contributing factor in endometrial tumorigenesis. Recent research has focused on molecular mechanisms involving proto-oncogenes and tumor suppressor genes that regulate cell proliferation and apoptosis. The Bcl-2 proto-oncogene, located on chromosome 18q21, inhibits

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apoptosis and prolongs cell survival, thereby playing a significant role in the development and progression of various epithelial malignancies. [3-5]

Antigen Ki-67 is a protein in humans which is encoded by the MKI 67 gene. Antigen Ki-67 is a nuclear protein that is associated with and may be necessary for cellular proliferation. The Ki-67 protein is a cellular marker for proliferation. Furthermore it is associated with ribosomal RNA transcription. Inactivation of antigen Ki-67 leads to inhibition of ribosomal RNA synthesis. [6-8] During interphase, the Ki-67 antigen can be exclusively detected within the cell nucleus, whereas in mitosis most of the protein is relocated to the surface of the chromosomes. Ki-67 protein is present during all active phases of the cell cycle (G_1, S, G_2, and mitosis), but is absent in resting cells (G_0). The fraction of Ki-67-positive tumor cells (the Ki-67 labelling index) is often correlated with the clinical course of cancer. The best-studied examples in this context are carcinomas of Endometrium, cervix, prostate, brain, breast and nephroblastoma. [9, 10] **We** studied the apoptotic and mitotic activity in endometrium immunohistochemically by applying Bcl-2, an anti-apoptotic marker and Ki-67, a cell proliferation marker in normal cyclical endometrium, endometrial hyperplasia and endometrial carcinoma.

Materials and Methods

This descriptive study (retrospective and prospective) was conducted in the Department of Pathology at Meenakshi Medical College Hospital and Research Institute (MMCH&RI), Enathur, Kanchipuram, Tamil Nadu, India, from January 2014 to April 2017. Institutional Ethics Committee approval was obtained prior to the study. A total of 60 endometrial tissue specimens were included and evaluated by a single histopathologist to avoid inter-observer variation.

Among the specimens, 26 were obtained from dilatation and curettage procedures and 34 from total abdominal hysterectomy with bilateral salpingo-oophorectomy. The mean age of the patients was 45 years. Patients who had received hormonal therapy within three menstrual cycles prior to surgery were excluded. All patients provided informed consent for the use of tissue samples for research purposes.

Histopathological examination was performed on hematoxylin and eosin stained sections. Of the 60 specimens, 15 cases were diagnosed as endometrial carcinoma, 25 as endometrial hyperplasia, 10 as proliferative phase endometrium, and 10 as secretory phase endometrium.

Immunohistochemistry was performed on formalin-fixed paraffin-embedded tissue sections (3–4 μm thick) using the Avidin–Biotin Complex method. Mouse monoclonal anti-Ki-67 antibody and rabbit monoclonal anti-Bcl-2 antibody were used as primary antibodies. Antigen retrieval was performed using EDTA buffer (pH 9.0), and staining was visualized using diaminobenzidine (DAB) chromogen. Tonsil tissue served as positive control, while adipose tissue and reactive lymph node were used as negative controls.

The proportion of positively stained cells was evaluated in 10 high-power fields. Immunostaining was graded based on staining intensity and proportion of positive cells, and a weighted score was calculated.

Statistical analysis was performed using SPSS version 21.0. Chi-square test, ANOVA, Bonferroni test, and Mann–Whitney U test were applied to assess differences between groups. A p-value <0.05 was considered statistically significant.

RESULTS

EXPRESSION OF BCL-2 IN VARIOUS ENDOMETRIAL LESION AND CYCLICAL ENDOMETRIUM

In present study out of 60 cases, Bcl-2 expression was positive for 44 (73%) cases and negative for 16(27%) cases.

Out of 44 (73%) positive Bcl-2 cases, 10 (100%) cases were positive for proliferative endometrium, 4 (40%) cases were positive for secretory endometrium, 19 (76%) cases were positive for hyperplastic endometrium and 11 (73%) cases were positive for Endometrial Carcinoma.

Out of 16 (27%) Negative Bcl-2 cases, No case was negative for proliferative endometrium, 6 (60%) cases were negative for secretory endometrium, 6 (24%) cases negative for hyperplastic endometrium and 4 (27%) cases were negative for Endometrial Carcinoma.

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Table 1 - Expression of Bcl-2 in various Endometrial Lesion and Cyclical Endometrium

S. No	Endometrial lesion	Sample size	Negative		Positive	
			No.0f cases	Percentage	No of cases	Percentage
1	Proliferative phase	10	-	-	10	100%
2	Secretory phase	10	6	60%	4	40%
3	Hyperplasia	25	6	24%	19	76%
4	Endometrial carcinoma	15	4	27%	11	73%
	Total	60	16 (27%)		44 (73%)	

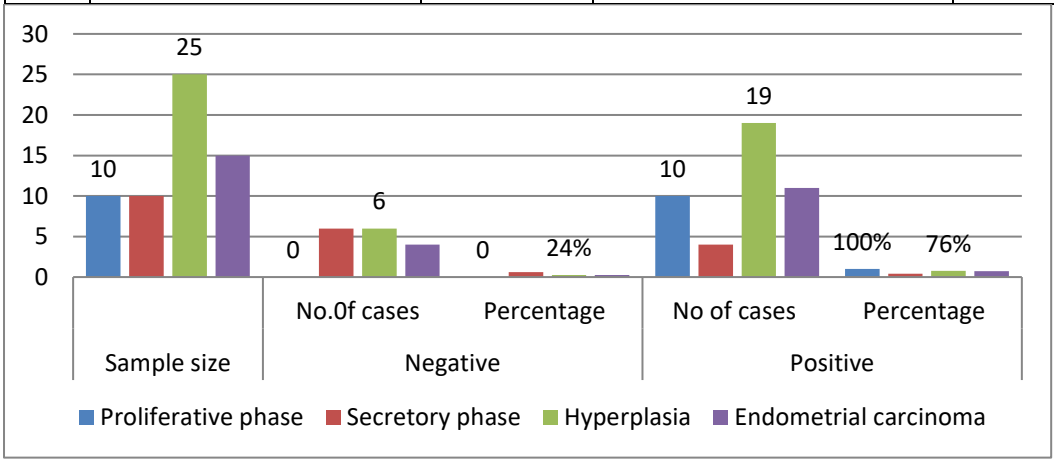

Figure 1 - Expression of Bcl-2 in various Endometrial Lesion and Cyclical Endometrium

EXPRESSION OF BCL-2 IN HYPERPLASIA

In present study out of 25 cases of Endometrial Hyperplasia, 15(60%) cases were Simple hyperplasia, 5 (20%) cases were Complex Hyperplasia without atypia and 5 (20%) cases were Complex hyperplasia with atypia.

In 15 cases of simple Hyperplasia, Bcl-2 expression was Positive for 12 (80%) cases and was Negative for 3 (20%) cases.

In 5 cases of Complex Hyperplasia without Atypia, Bcl-2 expression was Positive for 3 (60%) cases and was Negative for 2 (40%) cases.

In 5 cases of Complex Hyperplasia with Atypia, Bcl-2 expression was Positive for 4 (80%) cases and was Negative for 1 (20%) case.

Table 2 - Expression of Bcl-2 in Hyperplasia

S. No	Type of endometrium	Sample size	Negative		Positive	
			No. of cases	Percentage	No. of cases	Percentage
1	Simple hyperplasia without atypia	15 (60%)	3	20%	12	80%

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2	Complex hyperplasia without atypia	5 (20%)	2	40%	3	60%
3	Complex hyperplasia with atypia	5 (20%)	1	20%	4	80%
	Total	25	6 (24%)		19 (76%)	

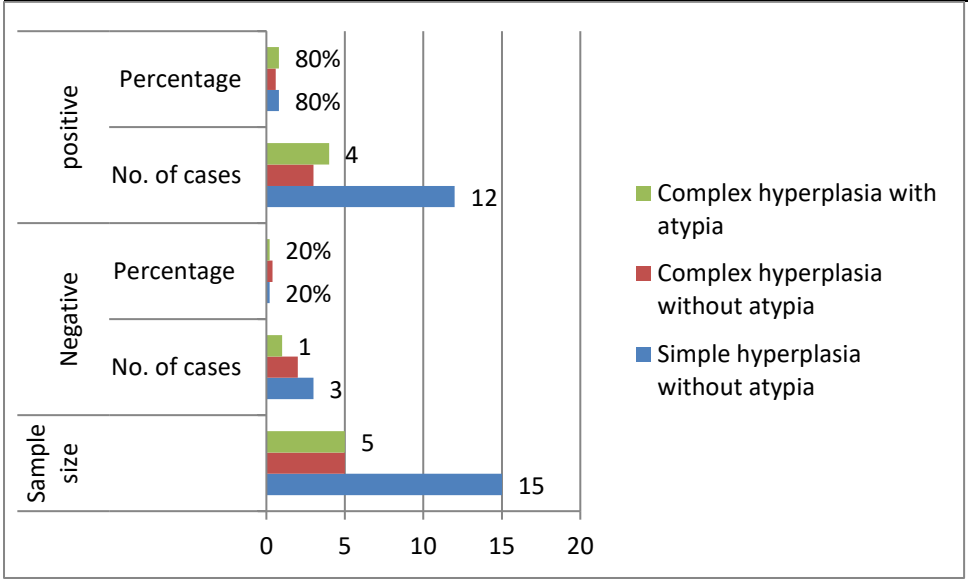

Figure 2 - Expression of Bcl-2 in Hyperplasia

COMPARSION OF Bcl-2 EXPRESSION IN CYCLICAL ENDOMETRIUM

In present study of 10 proliferative Endometrium for Bcl-2 expression, 2 (20%) cases show 1+ expression, 3 (30%) cases show 2+ expression, 3 (30%) cases show 3+ expression and 2 (20%) cases shows 4+ expression.

In present study of 10 Secretory Endometrium for Bcl-2 expression, 2 (20%)cases shows 1+ expression, 2 (20%) cases show 2+ expression, 6 (60%) cases show no expression.

Table 3 - Comparison of Bcl-2 Expression in Cyclical Endometrium

SCORE	**CYCLICAL ENDOMETRIUM**	
	PROLIFERATIVE PHASE	**SECRETORY PHASE**
0	-	6(60%)
1+	2(20%)	2(20%)
2+	3(30%)	2(20%)
3+	3(30%)	-
4+	2(20%)	-
TOTAL	**10**	**10**

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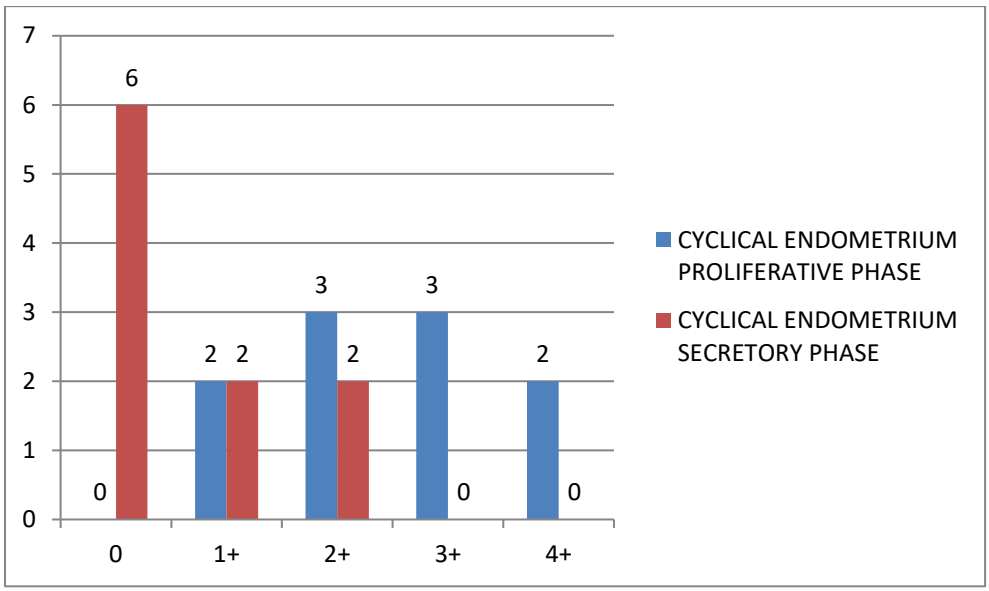

Figure 3- Comparison of Bcl-2 Expression in Cyclical Endometrium

COMPARSION OF Bcl-2 EXPRESSION IN ENDOMETRIAL HYPERPLASIA AND CARCINOMA

In present study of 15 cases of simple hyperplasia for Bcl-2 expression, 3(20%) cases show no expression, 4 (27%) cases show expression of 1+, 3 (20%) cases show expression of 2+, 4(27%) cases show expression of 3+ and 1 (6%) case show expression of 4+. (SP vs SH p value = 0.03)

Out of 5 cases of complex hyperplasia without atypia, 2(40%) cases show no expression, 1 (20%) cases show expression of 2+, 1 (20%) case show expression of 3+, 1 (20%) case show expression of 4+. (PP vs CH with atypia p value = 0.7)

Out of 5 cases of complex hyperplasia with atypia, 1(20%) cases show no expression, 1 (20%) case show expression of 2+, 1 (20%) case show expression of 3+, 2 (40%) case show expression of 4+.

In present study of 15 cases of Endometrial Carcinoma for Bcl-2 expression, 4 (26%) cases show no expression, 3 (20%) show expression of 1+, 6 (40%) cases show expression of 2+, 1 (7%) case show expression of 3+ and 1 (7%) case show expression of 4+. No lymphnodes were included for the study. (SP vs CH with atypia p value = 0.04)

Table 4 - Comparison of Bcl-2 Expression in Endometrial Hyperplasia and Carcinoma

Score	Endometrial hyperplasia (n=25)			Endometrial carcinoma
	Simple hyperplasia	CH without Atypia	CH with Atypia	
0	3 (20%)	2 (40%)	1 (20%)	4 (26%)
1+	4 (27%)	0	0	3 (20%)
2+	3 (20%)	1 (20%)	1 (20%)	6 (40%)
3+	4 (27%)	1 (20%)	1 (20%)	1 (7%)
4+	1 (6%)	1 (20%)	2 (40%)	1 (7%)
TOTAL	**15**	**5**	**5**	**15**

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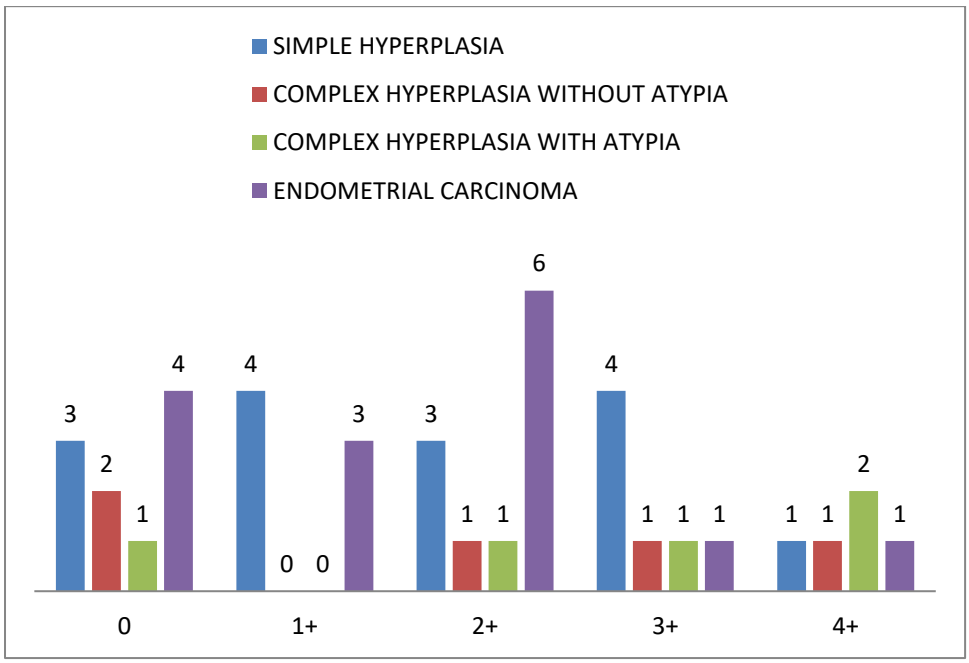

Figure 4: Comparison of Bcl-2 Expression in Endometrial Hyperplasia and Carcinoma

EXPRESSION OF Bcl-2 AMONG THE GROUPS

In present study for Bcl-2 expression, no expression was seen in 6(60%) cases of secretory endometrium, 3(20%) cases of simple hyperplasia, 2(40%) cases in complex hyperplasia without atypia and 1(20%) in complex hyperplasia with atypia and 4 (26%) cases in Endometrial Carcinoma. (SP vs CA p value = 0.08)

Weak positivity (1+ &2+) for Bcl-2 expression was seen in 5(50%) cases in proliferative endometrium, 4(40%) cases in secretory endometrium, 7(47%) cases of simple hyperplasia, 1(20%) case in complex hyperplasia without atypia and 1(20%) case in complex hyperplasia with atypia and 9(60%) cases in endometrial Carcinoma. (PP vs CA p value = 0.48)

Strong Positivity (3+& 4+) for Bcl-2 expression was seen in 5(50%) cases in proliferative endometrium, no cases in secretory endometrium, 5(33%) cases of simple hyperplasia, 2(40%) case in complex hyperplasia without atypia and 3(60%) case in complex hyperplasia with atypia and 2(14%) cases in Endometrial Carcinoma. (SP vs CH with atypia p value = 0.05)

Table 5 - Expression of Bcl-2 among the Groups

Score	Cyclical endometrium		Endometrial hyperplasia (n=25)			Endometrial carcinoma
	Proliferative phase	Secretory phase	Simple hyperplasia	CH without Atypia	CH with Atypia	
0	-	6(60%)	3 (20%)	2 (40%)	1 (20%)	4 (26%)
1+	2(20%)	2(20%)	4 (27%)	0	0	3 (20%)
2+	3(30%)	2(20%)	3 (20%)	1 (20%)	1 (20%)	6 (40%)
3+	3(30%)	-	4 (27%)	1 (20%)	1 (20%)	1 (7%)

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4+	2(20%)	-	1 (6%)	1 (20%)	2 (40%)	1 (7%)
TOTAL	**10**	**10**	**15**	**5**	**5**	**15**

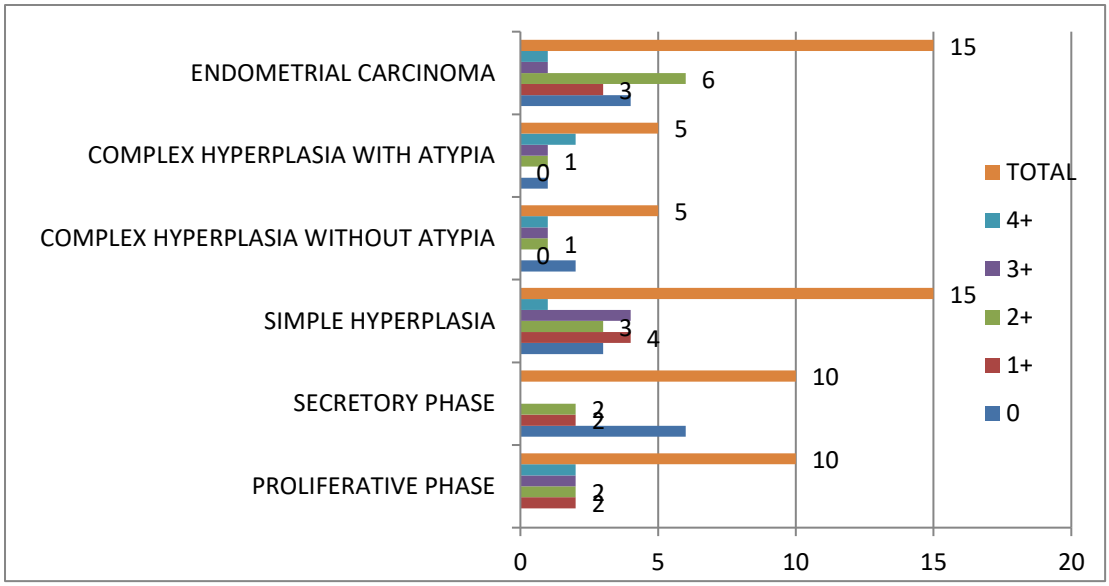

Figure 5- Expression of Bcl-2 among the Groups

EXPRESSION OF KI-67 IN VARIOUS ENDOMETRIAL LESION AND CYCLICAL ENDOMETRIUM

In present study out of 60 cases, Ki-67 expression was positive for 42 (70%) cases and negative for 18(30%) cases.

Out of 42 (70%) positive Ki-67 cases, 7 (70%) cases were positive for proliferative endometrium, 4 (40%) cases were positive for secretory endometrium, 19 (76%) cases were positive for hyperplastic endometrium and 12 (80%) cases were positive for Endometrial Carcinoma.

Out of 18 (30%) Negative Ki-67 cases, 3 (30%) cases were negative for proliferative endometrium, 6 (60%) cases were negative for secretory endometrium, 6 (24%) cases negative for hyperplastic endometrium and 3 (20%) cases were negative for Endometrial Carcinoma.

Table 6 - Expression of Ki-67 in various Endometrial Lesion and Cyclical Endometrium

S. No	**Endometrial lesion**	**Sample size**	**Negative**		**Positive**	
			No.0f cases	**Percentage**	**No of cases**	**Percentage**
1	Proliferative phase	10	3	30%	7	70%
2	Secretory phase	10	6	60%	4	40%
3	Hyperplasia	25	6	24%	19	76%
4	Endometrial carcinoma	15	3	20%	12	80%
	Total	60	18 (30%)		42 (70%)	

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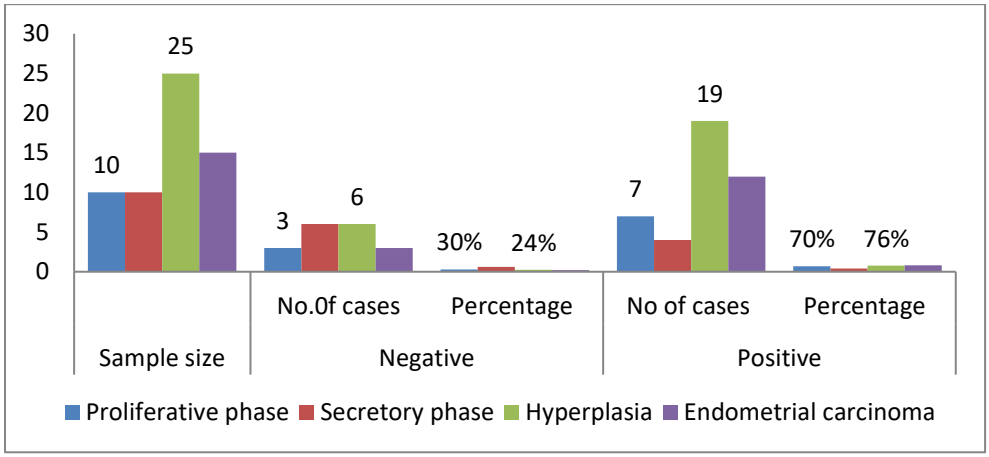

Figure 6- Expression of Ki-67 in Various Endometrial Lesion & Cyclical Endometrium

EXPRESSION OF KI-67 IN HYPERPLASIA

In present study out of 25 cases of Endometrial Hyperplasia, 15(60%) cases were Simple hyperplasia, 5 (20%) cases were Complex Hyperplasia without atypia and 5 (20%) cases were Complex hyperplasia with atypia.

In 15 cases of simple Hyperplasia, Ki-67 expression was Positive for 12 (80%) cases and was Negative for 3 (20%) cases.

In 5 cases of Complex Hyperplasia without Atypia, Ki-67 expression was Positive for 3 (60%) cases and was Negative for 2 (40%) cases.

In 5 cases of Complex Hyperplasia with Atypia, Ki-67 expression was Positive for 4 (80%) cases and was Negative for 1 (20%) case.

Table 7 - Expression of Ki-67 in Hyperplasia

S. No	Type of endometrium	Sample size	Negative		Positive	
			No. of cases	Percentage	No. of cases	Percentage
1	Simple hyperplasia without atypia	15	3	20%	12	80%
2	Complex hyperplasia without atypia	5	2	40%	3	60%
3	Complex hyperplasia with atypia	5	1	20%	4	80%
	Total	25	6		19	

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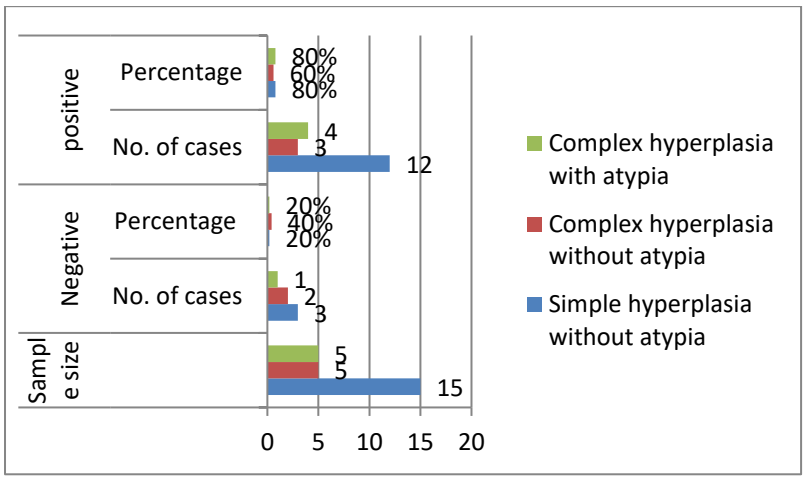

Figure 7 - Expression of Ki-67 in Hyperplasia

COMPARSION OF Ki-67 EXPRESSION IN CYCLICAL ENDOMETRIUM

In present study of 10 proliferative Endometrium for Ki-67 expression, 6 (60%) cases show 1+ expression, 1 (10%) case show 2+ expression and 3 (30%) cases shows no expression. (PP vs CH with atypia p value = 0.004)

In present study of 10 Secretory Endometrium for Ki-67 expression, 3 (30%) cases show 1+ expression, 1 (10%) case show 2+ expression, 6 (60%) cases show no expression. (SP vs CH with atypia p value = 0.002)

Table 8 - Comparison of Ki-67 Expression in Cyclical Endometrium

Score	Cyclical endometrium	
	Proliferative phase	**Secretory phase**
0	3 (30%)	6 (60%)
1+	6 (60%)	3 (30%)
2+	1 (10%)	1 (10%)
3+	0	0
4+	0	0
TOTAL	**10**	**10**

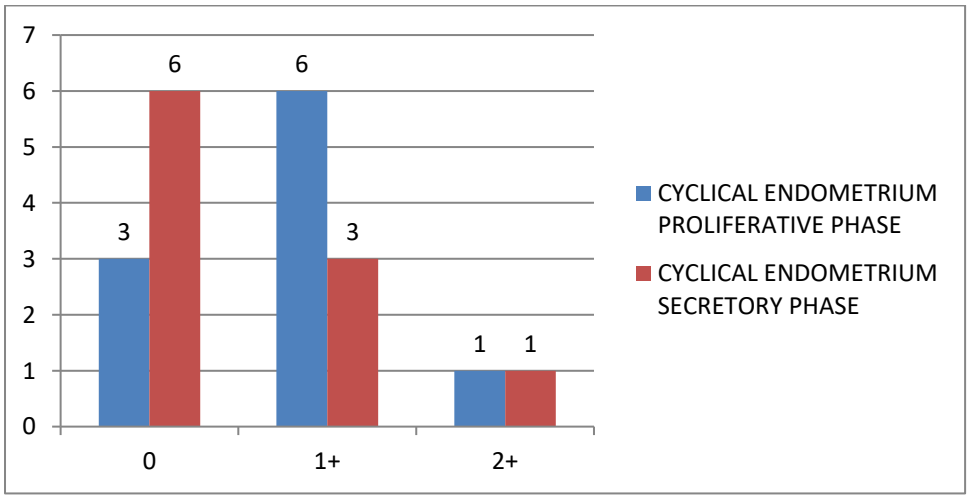

Figure 8 - Comparison of Ki-67 Expression in Cyclical Endometrium

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COMPARSION OF Ki-67 EXPRESSION IN ENDOMETRIAL HYPERPLASIA AND CARCINOMA

In present study of 15 cases of simple hyperplasia for Ki-67 expression, 3(20%) cases show no expression, 8 (53%) cases show expression of 1+, 3 (20%) cases show expression of 2+, No cases show expression of 3+ and 1 (7%) case show expression of 4+.

Out of 5 cases of complex hyperplasia without atypia, 2(40%) cases show no expression, 2 (40%) cases show expression of 1+, 1 (20%) case show expression of 2+.

Out of 5 cases of complex hyperplasia with atypia, 1(20%) case show no expression, 3 (60%) cases show expression of 3+, 1 (20%) case show expression of 4+. (CH without atypia vs CH with atypia p value = 0.02)

In present study of 15 cases of Endometrial Carcinoma for Ki-67 expression, 3 (20%) cases show no expression, 5 (33%) cases show expression of 1+, 4 (27%) cases show expression of 2+, 2 (13%) cases show expression of 3+ and 1 (7%) case show expression of 4+. No lymph nodes were included for the study.

Table 9 - Comparison of Ki-67 Expression in Endometrial Hyperplasia and Carcinoma

Score	Endometrial hyperplasia (n=25)			Endometrial carcinoma
	Simple hyperplasia	CH without atypia	CH with atypia	
0	3 (20%)	2 (40%)	1 (20%)	3 (20%)
1+	8 (53%)	2 (40%)	0	5 (33%)
2+	3 (20%)	1 (20%)	0	4 (27%)
3+	0	0	3 (60%)	2 (13%)
4+	1 (7%)	0	1 (20%)	1 (7%)
TOTAL	**15**	**5**	**5**	**15**

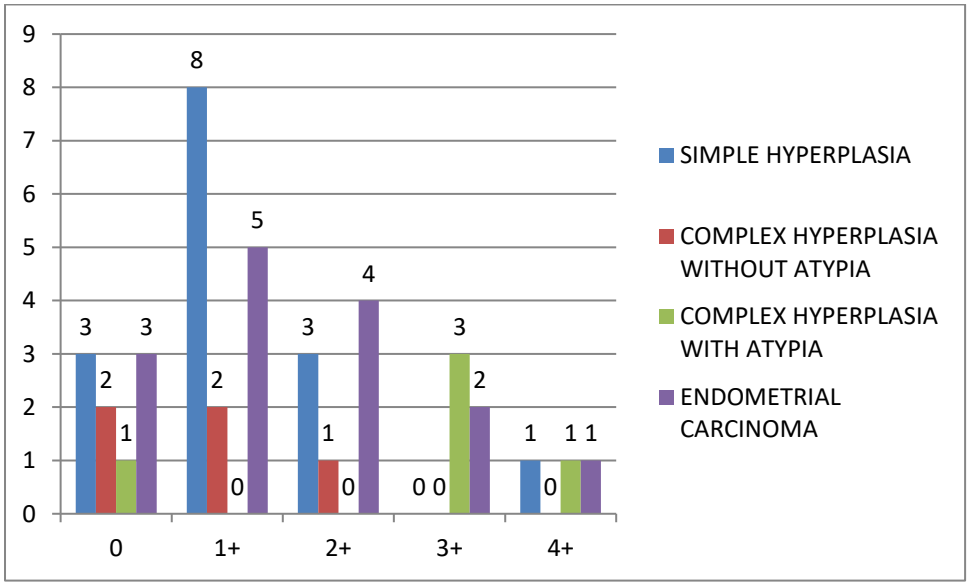

Figure 9 - Comparison of Ki-67 Expression in Endometrial Hyperplasia and Carcinoma

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EXPRESSION OF Ki-67 AMONG THE GROUPS:

In present study for Ki-67 expression, no expression was seen in 3(30%) cases of proliferative endometrium, 6(60%) cases of secretory endometrium, 3(20%) cases of simple hyperplasia, 2(40%) cases in complex hyperplasia without atypia and 1(20%) case in complex hyperplasia with atypia and 3 (20%) cases in Endometrial Carcinoma. (PP vs CA p value = 0.12)

Weak positivity (1+ &2+) for Ki-67 expression was seen in 7(70%) cases in proliferative endometrium, 4(40%) cases in secretory endometrium, 11(73%) cases of simple hyperplasia, 3(60%) cases in complex hyperplasia without atypia and No cases in complex hyperplasia with atypia and 9(60%) cases in endometrial Carcinoma. (SP vs CA p value = 0.02)

Strong Positivity (3+& 4+) for Ki-67 expression was seen in 1(7%) case of simple hyperplasia, 4(80%) case in complex hyperplasia with atypia and 3(20%) cases in Endometrial Carcinoma. No strong positivity cases were seen in Proliferative endometrium, Secretory endometrium and Complex hyperplasia without atypia

TABLE 10: EXPRESSION OF Ki-67 AMONG THE GROUPS:

Score	Cyclical endometrium		Endometrial hyperplasia (n=25)			Endometrial carcinoma
	Proliferative phase	Secretory phase	SH	CH without atypia	CH with atypia	
0	3 (30%)	6 (60%)	3 (20%)	2 (40%)	1 (20%)	3 (20%)
1+	6 (60%)	3 (30%)	8 (53%)	2 (40%)	0	5 (33%)
2+	1 (10%)	1 (10%)	3 (20%)	1 (20%)	0	4 (27%)
3+	0	0	0	0	3 (60%)	2 (13%)
4+	0	0	1 (7%)	0	1 (20%)	1 (7%)
TOTAL	**10**	**10**	**15**	**5**	**5**	**15**

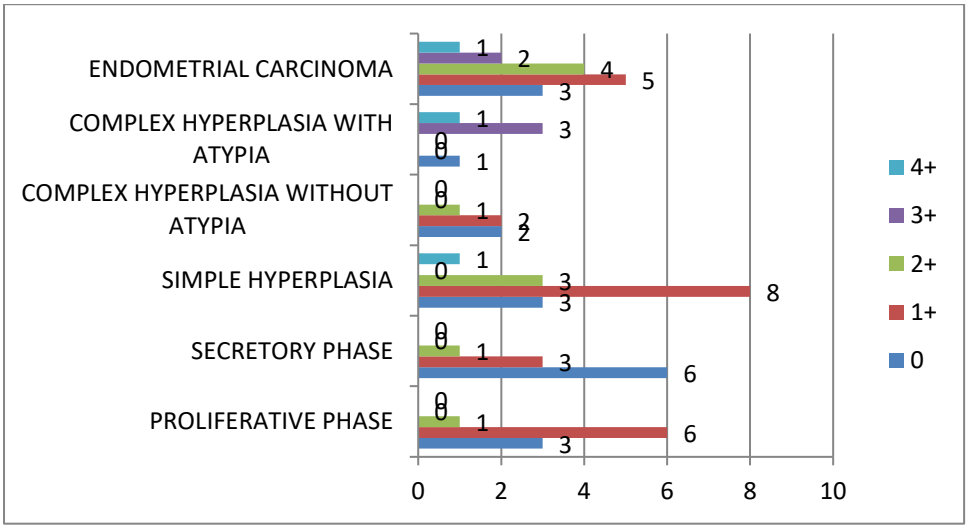

Figure 10 - Expression of Ki-67 among the Groups

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COMPARSION OF EXPRESSION OF KI-67 AND BCL-2

Out of 10 proliferative endometrium cases, 10 (100%) cases were positive for Bcl-2 and 7(70%) cases were positive for Ki-67. Out of 10 secretory endometrium cases, 4(40%) cases were positive for Bcl-2 and Ki-67.

Out of 10 proliferative endometrium cases, No cases were negative for Bcl-2 and 3(30%) cases were Negative for Ki-67. Out of 10 secretory endometrium cases, 6(60%) cases were Negative for Bcl-2 andKi-67.

Out of 25 Endometrial hyperplasia cases, 19 (76%) cases were positive for Bcl-2 and Ki-67. Out of 15 Endometrial carcinoma, 11(73%) cases were positive for Bcl-2 and 12 (80%) cases were positive for Ki-67.

Out of 25 Endometrial hyperplasia cases, 6 (24%) cases were Negative for Bcl-2 and Ki-67. Out of 15 Endometrial carcinoma, 4(27%) cases were Negative for Bcl-2 and 3 (20%) cases were Negative for Ki-67.

Table 11 - Comparison of Expression of KI-67 and BCL-2

S. No	Endometrial lesion	Sample size	Positive Cases		Negative Cases	
			Bcl-2	Ki-67	Bcl-2	Ki-67
1	Proliferative phase	10	10 (100%)	7 (70%)	0	3 (30%)
2	Secretory phase	10	4 (40%)	4 (40%)	6 (60%)	6 (60%)
3	Hyperplasia	25	19 (76%)	19 (76%)	6 (24%)	6 (24%)
4	Endometrial carcinoma	15	11 (73%)	12 (80%)	4 (27%)	3 (20%)
	Total	60	44	42	16	18

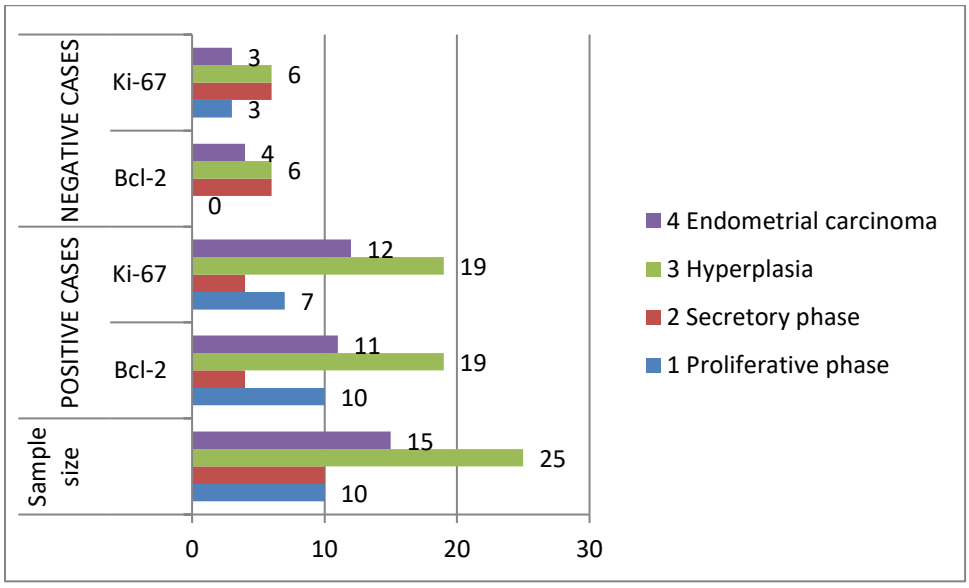

Figure 11 - Comparison of Expression of KI-67 and BCL-2

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COMPARSION OF Bcl-2 AND Ki-67 EXPRESSION IN CYCLICAL ENDOMETRIUM

In present study of 10 cases of proliferative endometrium, no negative cases of Bcl-2 is noted whereas 3(30%) case were negative for Ki-67 expression. Weak positive expression (1+&2+) of Bcl-2 is seen in 5 (50%) cases and 7(70%) cases were weak positive for Ki-67 expression. Strong positive expression (3+&4+) of Bcl-2 is seen in 5(50%) cases and no cases of Ki-67 shows strong Positivity.

Out of 10 cases of Secretory endometrium, Negative expression is seen in 6(60%) cases of Bcl-2 and Ki-67. Weak positive expression (1+&2+) is seen in 4 (40%) cases of Bcl-2 and Ki-67. No strong positive expression (3+&4+) for Bcl-2 and Ki-67 is seen.

Table 12 - Comparison of BCL-2 and KI-67 Expression in Cyclical Endometrium

Score	Proliferative Phase		Secretory Phase	
	Bcl-2	Ki-67	Bcl-2	Ki-67
0	-	3 (30%)	6(60%)	6 (60%)
1+	2(20%)	6 (60%)	2(20%)	3 (30%)
2+	3(30%)	1 (10%)	2(20%)	1 (10%)
3+	3(30%)	0	-	0
4+	2(20%)	0	-	0
TOTAL	**10**	**10**	**10**	**10**

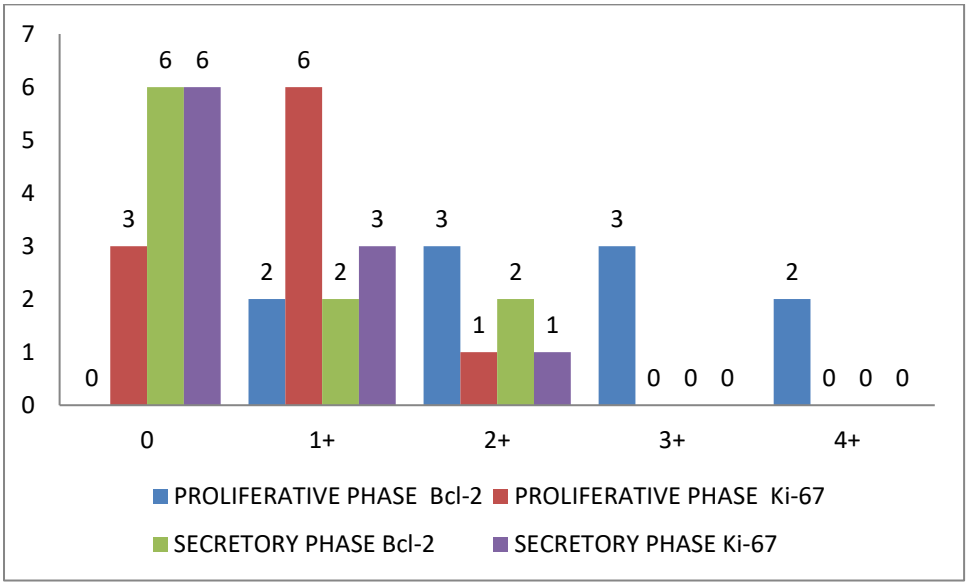

Figure 12- Comparison of BCL-2 and KI-67 Expression in Cyclical Endometrium

COMPARSION OF Bcl-2 AND KI-67 IN HYPERPLASIA CASES

In present study of 15 cases of simple hyperplasia, Negative expression for Bcl-2 and Ki-67 is seen in 3(20%) cases each. Weak positivity (1+&2+) expression for Bcl-2 was seen in 7(47%) cases and 11(73%) cases were weak positive for Ki-67 expression. Strong positivity (3+&4+) expression for Bcl-2 was seen

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in 5(33%) cases and 1(7%) case was strong positive for Ki-67 expression.

Out of 5 cases of complex hyperplasia without Atypia, Negative expression for Bcl-2 and Ki-67 is seen in 2(40%) cases each. Weak positivity (1+&2+) expression for Bcl-2 was seen in 1(20%) case and 3(60%) cases were weak positive for Ki-67 expression. Strong positivity (3+&4+) expression for Bcl-2 was seen in 2(40%) cases and No cases were strong positive for Ki-67 expression.

Out of 5 cases of complex hyperplasia with Atypia, Negative expression for Bcl-2 and Ki-67 is seen in 1(20%) case each. Weak positivity (1+&2+) expression for Bcl-2 was seen in 1(20%) case and No cases were weak positive for Ki-67 expression. Strong positivity (3+&4+) expression for Bcl-2 was seen in 3(60%) and 4(80%) cases were strong positive for Ki-67 expression.

Table 13: Comparison of BCL-2 and KI-67 in hyperplasia cases

Score	**Simple hyperplasia**		**Complex hyperplasia Without atypia**		**Complex hyperplasia With atypia**	
	Bcl-2	Ki-67	Bcl-2	Ki-67	Bcl-2	Ki-67
0	3 (20%)	3 (20%)	2 (40%)	2 (40%)	1 (20%)	1 (20%)
1+	4 (27%)	8 (53%)	0	2 (40%)	0	0
2+	3 (20%)	3 (20%)	1 (20%)	1 (20%)	1 (20%)	0
3+	4 (27%)	0	1 (20%)	0	1 (20%)	3 (60%)
4+	1 (6%)	1 (7%)	1 (20%)	0	2 (40%)	1 (20%)
TOTAL	**15**	**15**	**5**	**5**	**5**	**5**

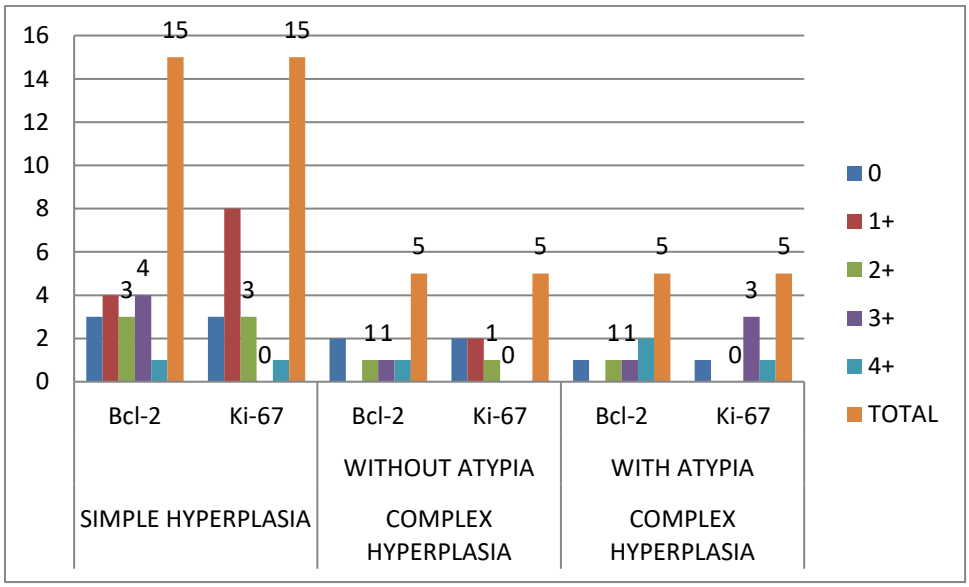

Figure 13 - Comparison of BCL-2 and KI-67 in hyperplasia cases

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COMPARSION OF Bcl-2 AND Ki-67 EXPRESSION IN ENDOMETRIAL HYPERPLASIA AND CARCINOMA

In present study of 25 cases of Endometrial hyperplasia, Negative expression for Bcl-2 and Ki-67 is seen in 6(24%) cases each. Weak positivity (1+&2+) expression for Bcl-2 was seen in 9(36%) cases and 14(56%) cases were weak positive for Ki-67 expression. Strong positivity (3+&4+) expression for Bcl-2 was seen in 10(40%) and 5(20%) cases were strong positive for Ki-67 expression.

Out of 15 cases of Endometrial Carcinoma, Negative expression for Bcl-2 is seen in 4(26%) cases and 3 (20%) cases were negative for Ki-67 expression. Weak positivity (1+&2+) expression for Bcl-2 and Ki-67 was seen in 9(60%) cases each. Strong positivity (3+&4+) expression for Bcl-2 was seen in 2(14%) and 3(20%) cases were strong positive for Ki-67 expression.

Table 14 - Comparsion Of Bcl-2 And Ki-67 Expression In Endometrial Hyperplasia And Carcinoma

Score	Endometrial hyperplasia		Endometrial carcinoma	
	Bcl-2	Ki-67	Bcl-2	Ki-67
0	6 (24%)	6 (24%)	4 (26%)	3 (20%)
1+	4 (16%)	10 (40%)	3 (20%)	5 (33%)
2+	5 (20%)	4 (16%)	6 (40%)	4 (27%)
3+	6 (24%)	3 (12%)	1 (7%)	2 (13%)
4+	4 (16%)	2 (8%)	1 (7%)	1 (7%)
TOTAL	**25**	**25**	**15**	**15**

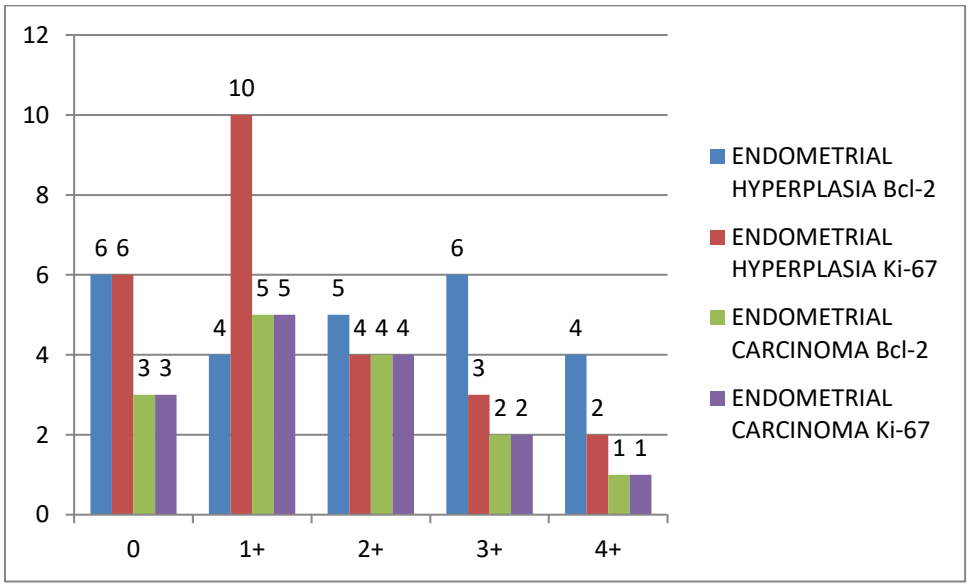

Figure 14 - Comparison of Bcl-2 & Ki-67 Expression in Endometrial Hyperplasia and Carcinoma

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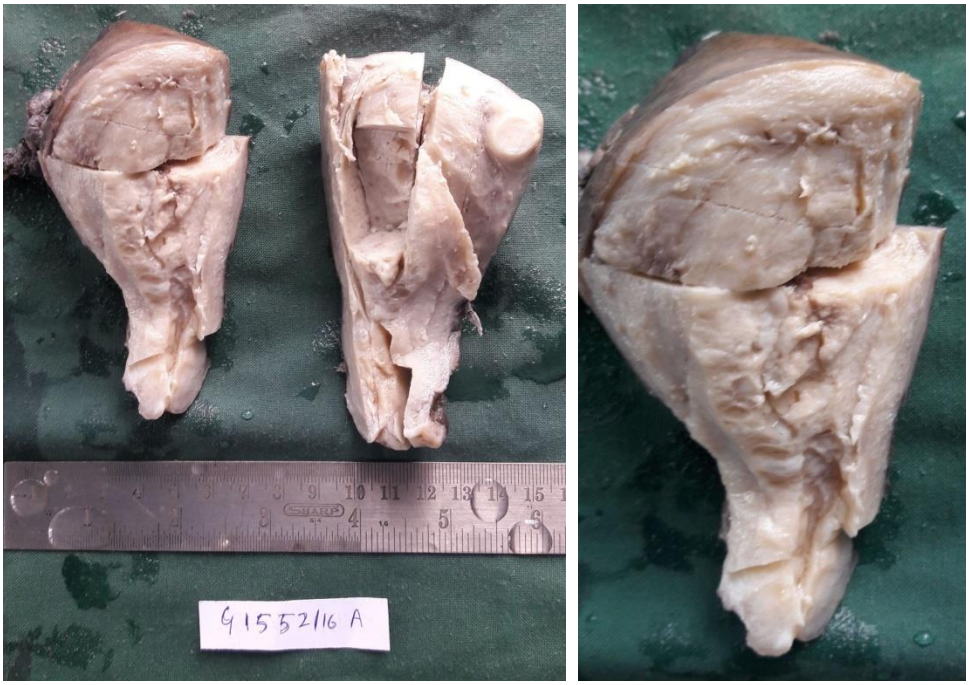

Figure 39 - Photograph of Gross Image of Endometrial Carcinoma

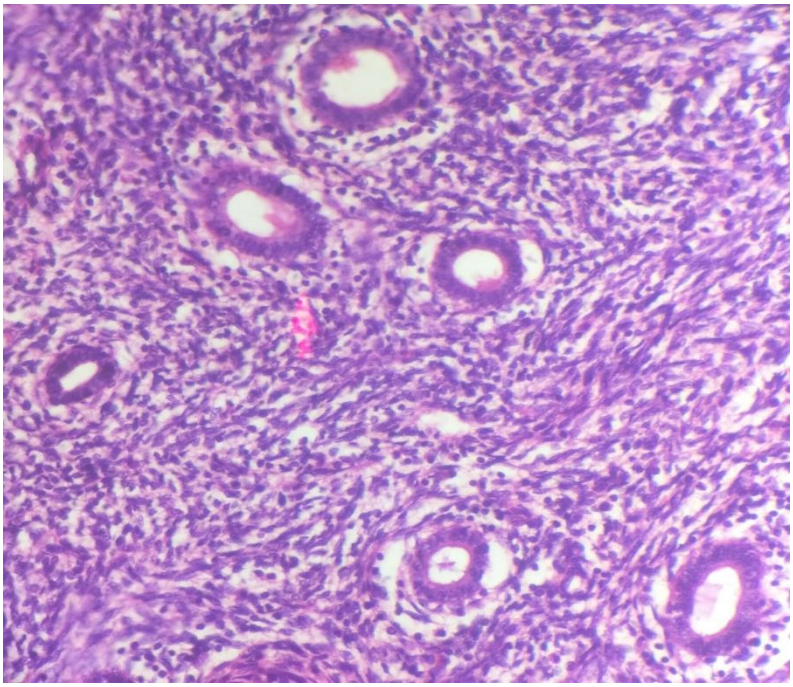

Figure 40 - Photomicrograph of Proliferative Phase, 40X (H&E)

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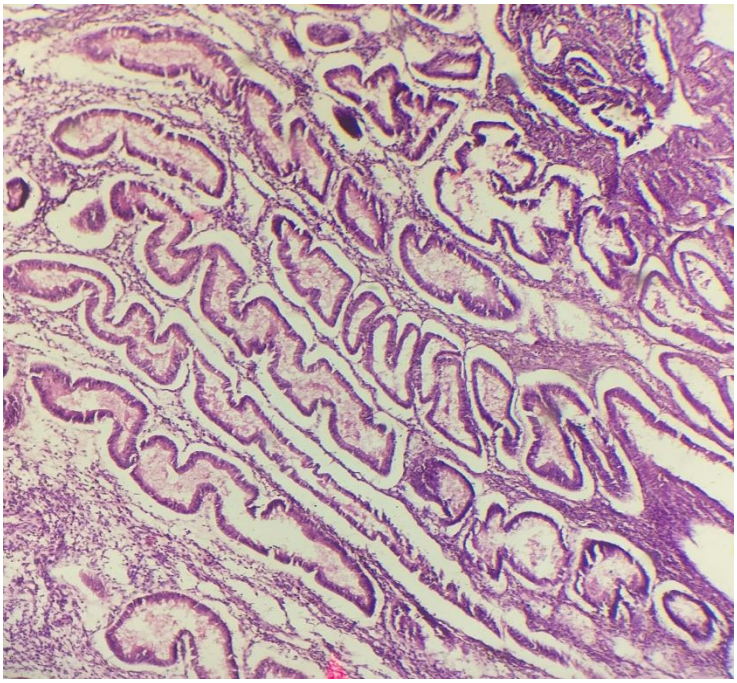

Figure 41 - Photomicrograph of Secretory Phase, 10X (H&E)

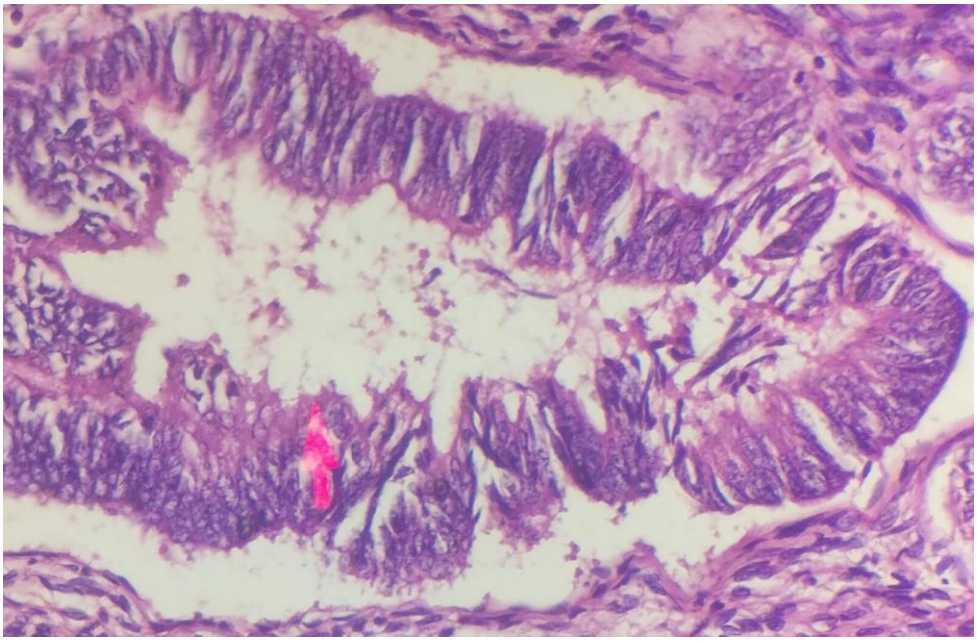

Figure 42 - Photomicrograph of Complex Hyperplasia with atypia, 40X (H&E)

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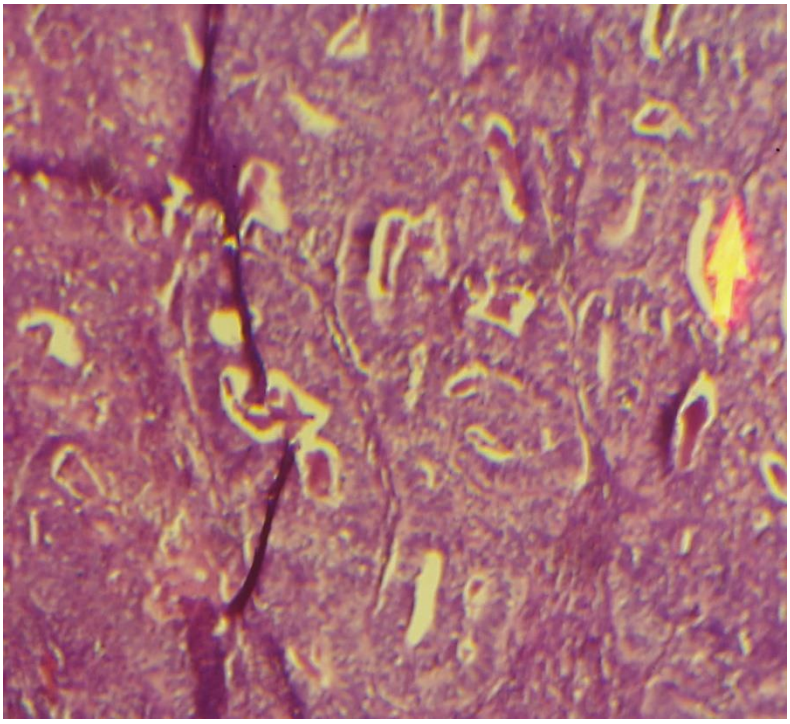

Figure 43 - Photomicrograph of Endometrial Carcinoma, 10X (H&E)

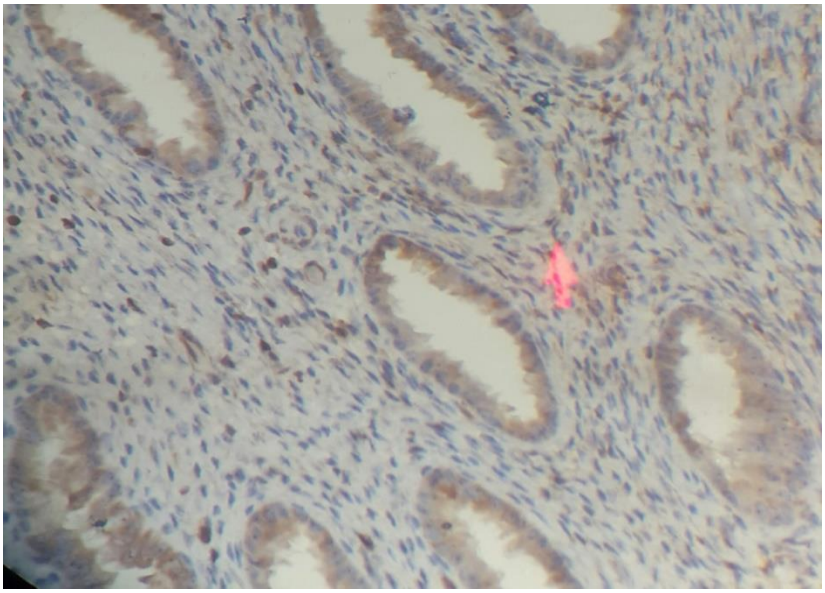

Figure 44 - Photomicrograph of Proliferative Phase, 10X

(IHC-Bcl-2 SCORE 2+)

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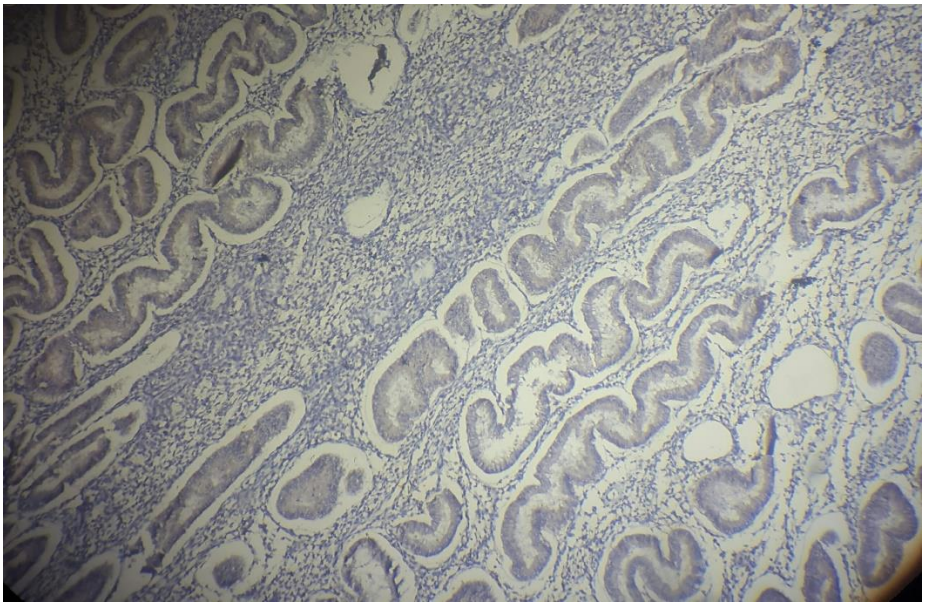

Figure 45 - Photomicrograph of Secretory Phase, 4X (IHC-Bcl-2 SCORE 1+)

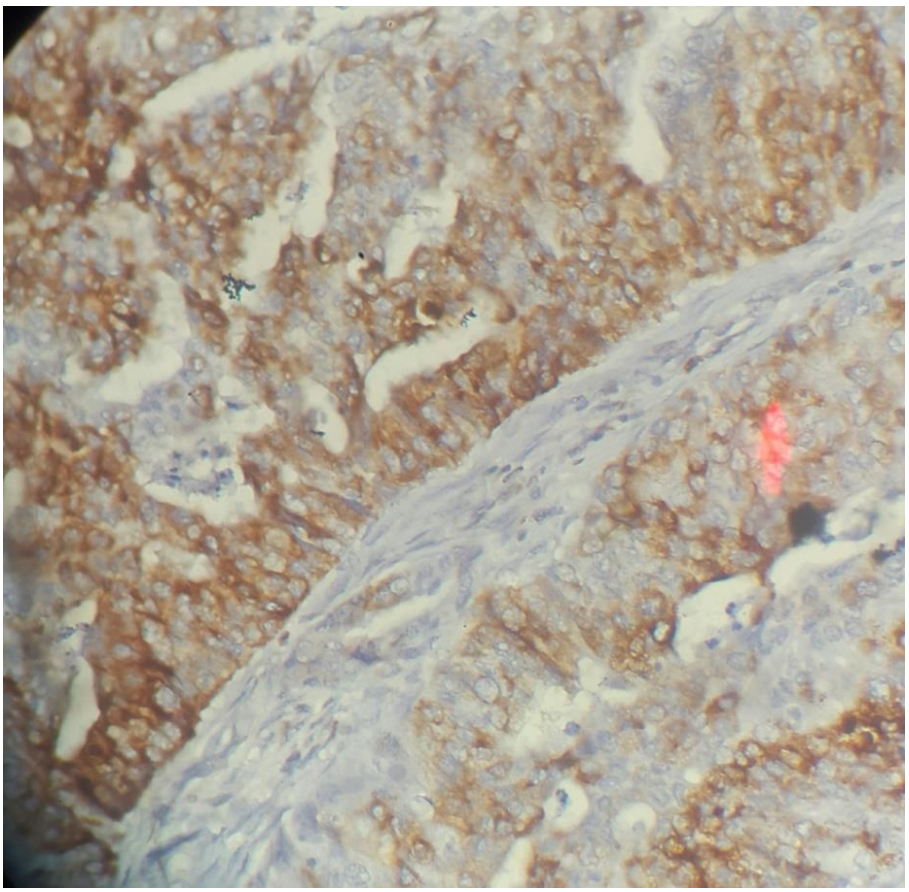

Figure 46 - Photomicrograph Of complex Hyperplasia with atypia, 40X (IHC-Bcl-2 SCORE 3+)

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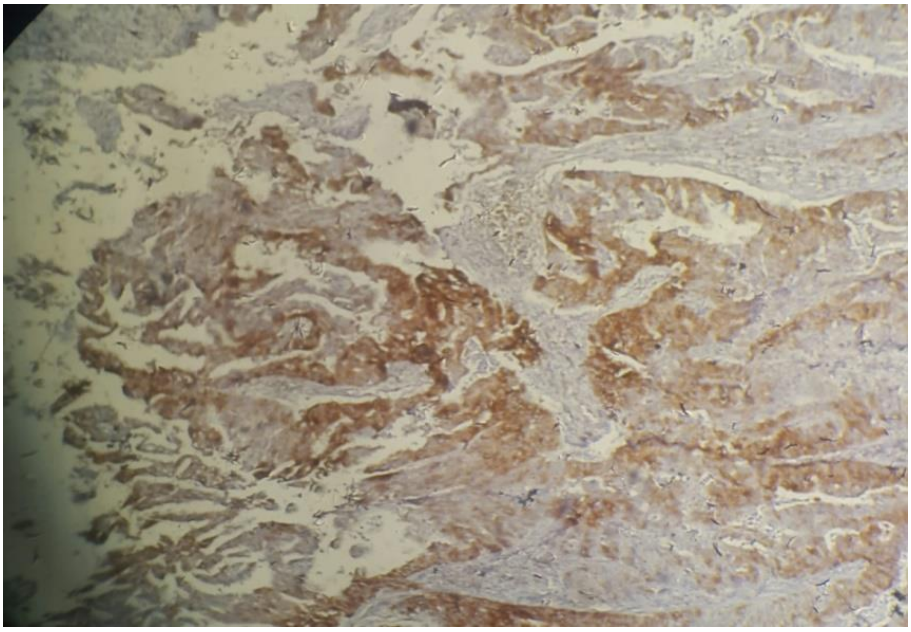

Figure 47 - Photomicrograph of Endometrial Carcinoma, 10X

(IHC-Bcl-2 SCORE 3+)

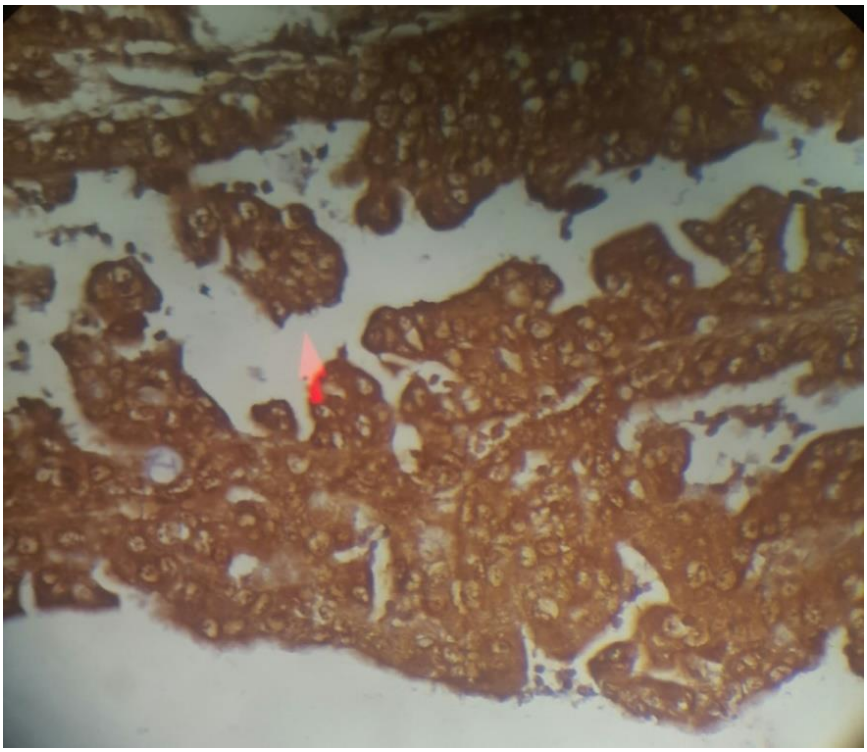

Figure 48 - Photomicrograph of Endometrial Carcinoma, 40X

(IHC-Bcl-2 SCORE 4+)

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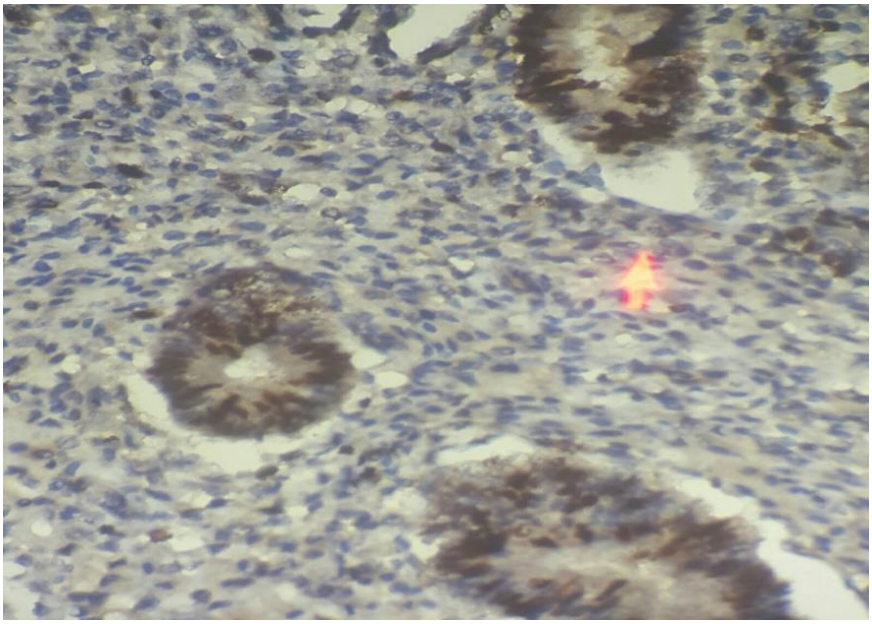

Figure 49 - Photomicrograph of Proliferative Phase, 40X

(IHC-Ki-67 SCORE 2+)

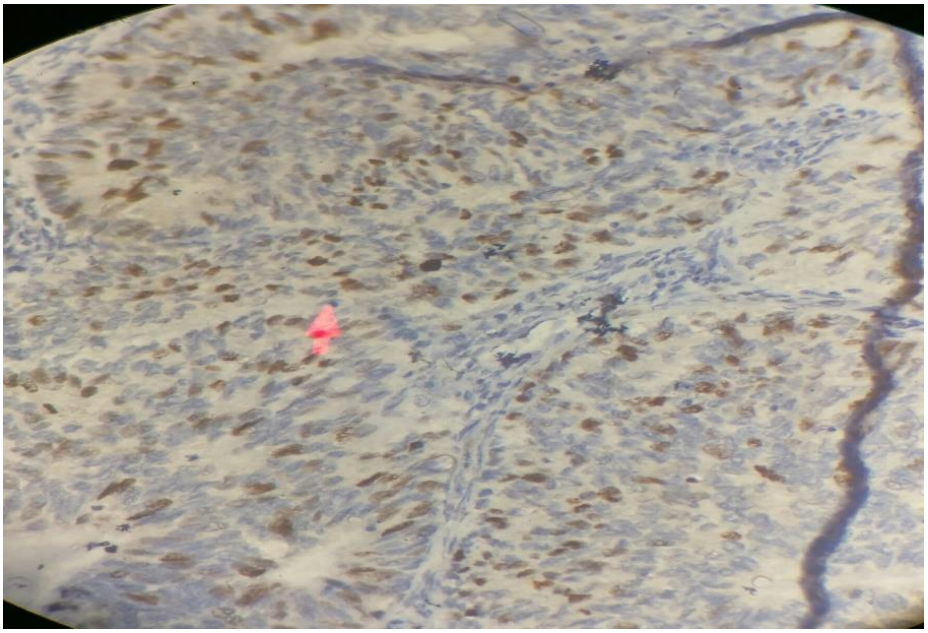

Figure 50 - Photomicrograph of Simple Hyperplasia, 10X

(IHC-KI-67 SCORE 2+)

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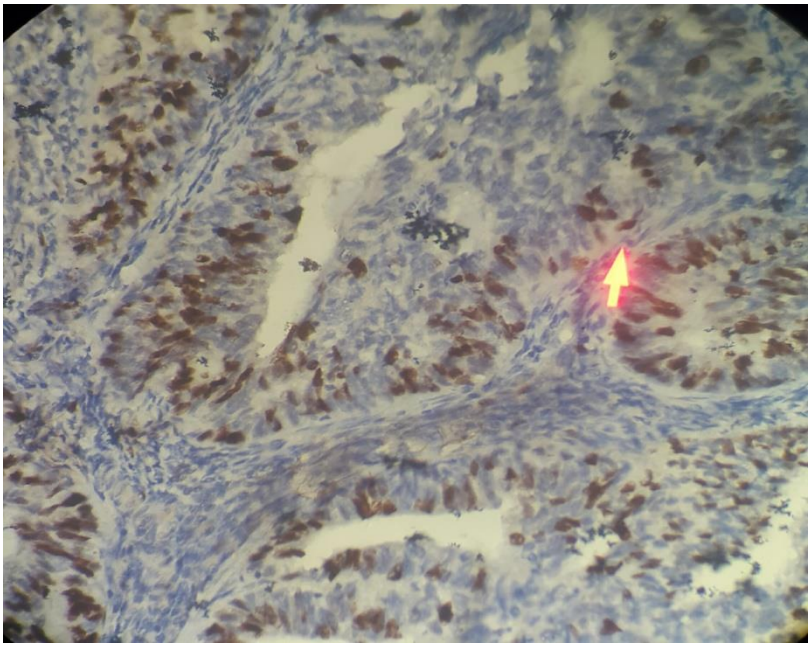

Figure 51 - Photomicrograph of Complex Hyperplasia with atypia, 10X

(IHC-KI-67 SCORE 3+)

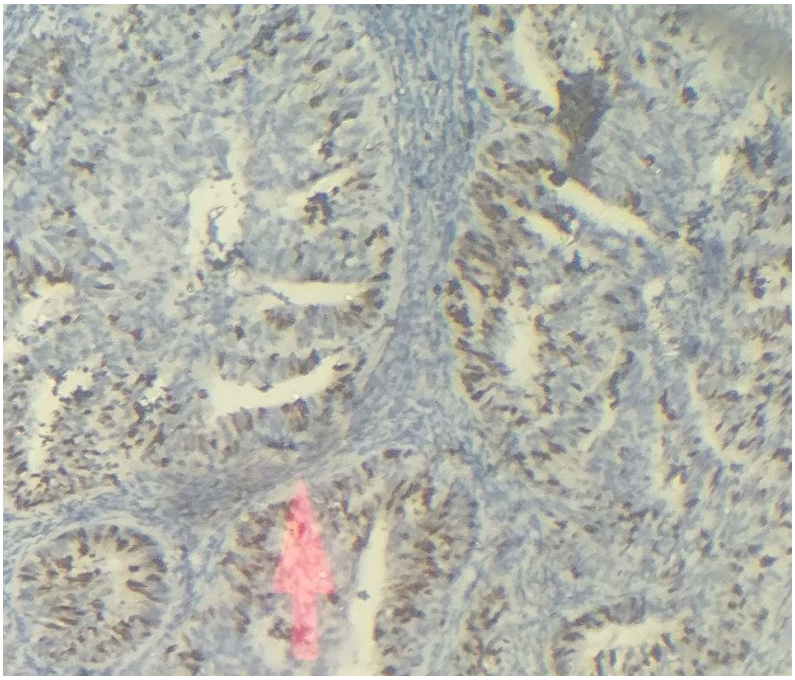

Figure 52 - Photomicrograph of Endometrial Carcinoma, 40X

(IHC-KI-67 SCORE 3+)

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DISCUSSION

Comparison of Bcl-2 Expression in Cyclical Endometrium

In the present study, **all proliferative endometrium cases showed Bcl-2 positivity**, with equal distribution of weak and strong staining, whereas **only 40% of secretory endometrium cases were positive**, all showing weak staining. This suggests a stronger estrogen-related anti-apoptotic activity during the proliferative phase. Similar findings were reported in earlier studies demonstrating increased Bcl-2 expression in proliferative endometrium with reduced expression during the secretory phase **(13–15)**. Other studies also reported peak Bcl-2 expression in the proliferative phase with a decline during the secretory phase **(11,12)**.

Comparison of Bcl-2 Expression in Endometrial Hyperplasia

In this study, **Bcl-2 positivity increased from simple hyperplasia to complex hyperplasia with atypia**, indicating progressive anti-apoptotic activity with increasing lesion severity. Similar observations were reported in previous studies **(16)**. However, some studies have reported decreased Bcl-2 expression in atypical hyperplasia **(17–19)**, which contrasts with the present findings.

Comparison of Bcl-2 Expression in Endometrial Carcinoma

All carcinoma cases were **endometrioid type Stage IA**, with Bcl-2 positivity observed in **74% of cases**. Expression was stronger in **well-differentiated tumors and decreased with increasing tumor grade**. Similar findings have been reported in earlier studies **(16,20,25)**. Increased Bcl-2 expression has also been associated with tumors showing **<50% myometrial invasion (21)**, while weak expression in carcinoma has been described in other reports **(17)**.

Comparison of Ki-67 Expression in Cyclical Endometrium

Ki-67 positivity was observed in **70% of proliferative endometrium cases and 40% of secretory endometrium cases**, with all cases showing weak positivity. No strong positivity was seen in cyclical endometrium. Similar findings demonstrating increased proliferative activity in the proliferative phase compared with the secretory phase have been reported **(14,15,22)**.

Comparison of Ki-67 Expression in Endometrial Hyperplasia

Ki-67 expression increased progressively from **simple hyperplasia to complex hyperplasia with atypia**, indicating an increasing proliferative index. Comparable findings have been reported in other studies **(23–25)**.

Comparison of Ki-67 Expression in Endometrial Carcinoma

In carcinoma cases, **Ki-67 expression was positive in 80%**, with **strong positivity mainly observed in poorly differentiated tumors** and absent in well-differentiated tumors. These findings suggest that Ki-67 expression correlates with tumor grade. Similar observations have been reported in previous studies evaluating proliferative markers in endometrial carcinoma **(23–25)**.

Comparison between Bcl-2 and Ki-67 Expression

The study demonstrated **progressively increased Bcl-2 expression in hyperplasia but reduced expression in high-grade carcinoma**, whereas **Ki-67 expression increased with lesion severity and tumor grade**, indicating higher proliferative activity. These findings support the concept that **Bcl-2 is associated with anti-apoptotic activity in early lesions, while Ki-67 reflects proliferative activity in advanced lesions**, which has also been reported in previous studies evaluating apoptotic and proliferative indices in endometrial lesions **(25)**.

CONCLUSION

In the present study, **Bcl-2 expression increased from simple hyperplasia to complex hyperplasia with atypia and was strongly positive in low-grade carcinomas but reduced in high-grade tumors**. In contrast, **Ki-67 expression showed strong positivity in complex hyperplasia with atypia and higher expression in high-grade carcinomas**, indicating increased proliferative activity. These findings suggest that **Bcl-2 may be involved in the progression from hyperplasia to carcinoma**, whereas **Ki-67 may serve as a useful prognostic marker due to its higher expression in aggressive tumors**. Thus, **Bcl-2 and Ki-67 can act as important diagnostic and prognostic markers in the progression of endometrial**

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hyperplasia to carcinoma. However, the study is limited by evaluation of only two immunohistochemical markers, and **further studies with larger sample sizes and additional markers such as ER, PR, and p53 are needed** for better understanding of endometrial tumorigenesis.

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