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Research Article

A Study of Bcl-2 and Ki-67 Expression in Endometrial Lesions at a Tertiary Care Centre

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ABSTRACT

INTRODUCTION: BCL-2 is B cell Lymphoma/Leukemia-2 protein encoded by BCL-2 gene which is located on Chromosome 18. BCL-2 is expressed in glandular and stromal cells of endometrium during the late proliferative phase and decreases in the late secretory phase and menstrual phase. Ki-67 is a protein found inside the cells and is most commonly seen during the cellular proliferation. During mitosis Ki-67 is detected in all the chromosomes, in all the cell cycle phases except in the G_0 phase or the resting phase.

AIM: To evaluate the expression of Ki-67 and Bcl-2, to assess the mitotic score and anti-apoptotic activity of the cyclical endometrium and endometrial lesions.

MATERIALS AND METHODS: This cross sectional study was done on all female patients of age 20-65 years undergoing endometrial curettage or biopsies for endometrial pathology was taken for assessment of Bcl-2 and Ki-67 immunohistochemistry.

RESULTS: Statistical analysis was done using student t test between Bcl-2 and Ki-67 assessment and significant association (p value <0.05) was found between Bcl-2 and Ki-67 expression in proliferative endometrium, atrophic endometrium and endometrial carcinoma.

CONCLUSION: Our study concludes that BCL2 and KI 67 shows significant association in endometrial cases. Bcl-2, an antiapoptotic marker expression was increased in hyperplasia cases and in atrophic endometrium which indicates less apoptosis. Ki-67 a marker for cell proliferation, expression was increased in proliferative phase and carcinoma cases indicating the presence of mitosis.

KEY WORDS: BCL2, KI67, Endometrium.

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INTRODUCTION

Endometrium is a complex multicellular membrane of the uterus that undergoes considerable growth and regression periodically (Henriet P et al.,2012, Petracco RG et al.,2012). It is completely regulated and controlled by hormones such as estrogen and progesterone which is responsible for maintenance of menstrual cycle and also plays a vital role in pregnancy (Singh M et al.,2011, Lessey BA et al.,2014). Pregnancy involves decidualization, implantation and placentation which are mainly coordinated by estrogen and

progesterone (Wang H et al., 2006, Dimitriadis E et al.,2010). In the absence of pregnancy, the decidua sheds off periodically in the endometrium (Ramathal CY et al.,2010, Evans J et al.,2016).

BCL-2 is B cell Lymphoma/Leukemia-2 protein encoded by BCL-2 gene which is located on Chromosome 18(Diebold J et al.,1996). BCL-2 is expressed in glandular and stromal cells of endometrium during the late proliferative phase and decreases in the late secretory phase and menstrual phase (Watanabe H et al.,1997, Konno R et al.,2000, Otsuki Y 2001). Smooth muscles of the myometrium cells show persistent BCL-2 immunoreactivity in the entire menstrual cycle which signifies that BCL-2 is essential for the survival of glandular cells of endometrium and also smooth muscle cells of uterine myometrium (Otsuki Y 2001).

Ki-67 is a protein found inside the cells and is most commonly seen during the cellular proliferation. During mitosis Ki-67 is detected in all the chromosomes, in all the cell cycle phases except in the G_0 phase or the resting phase (Gerdes J et al.,1983). Ki67 can only be detected in proliferating and dividing cells but it cannot be detected in quiescent cells (Gerlach C et al.,1997).During Mitosis Ki-67 levels increases in the early phases and tends to decrease in the later phases (Le Guellec S et al.,2011). Thus BCL-2 is related to the apoptosis regulation in the endometrium whereas Ki-67 is related to the mitotic activity in the endometrium. The aim of the study is to evaluate the expression of Ki-67 and Bcl-2, to assess the mitotic score and anti-apoptotic activity of the cyclical endometrium and endometrial lesions.

MATERIALS AND METHODS

This Cross sectional study was conducted at Department of Pathology at Shri Sathya Sai Medical College and Research Institute, a tertiary care hospital, Ammapettai, Chengalpattu during the period January 2020 to June 2021. Institute ethical clearance was obtained and IEC number was 2019/532. All female patients of age 20-65 years visiting our Obstetrics and Gynecology department and subsequently undergoing endometrial curettage or biopsies for endometrial pathology were included. Female patients of age less than 20 years and more than 65 years of age were excluded in the study. Pregnant women were also excluded in the study. Bcl-2 Score and Ki-67 Score were the study variables. Data was collected using predefined data capture format. Privacy and Confidentiality was maintained. All patient identifiable numbers and information was stripped and replaced by anonymous numbers. Sample size is 65 and calculation was done based on previous study(Masjeed NM et al.,2017). Sample size calculation was done as follows.

$n = 4pq/L^2$

where p is 75.71% (Ki-67)

q is 100-75.71% = 24.29

L is precision error 15% of prevalence in 11.36

n = 4 x 75.71 x 24.29/11.362

n = 7355.98/128.97

n = 57.04 + 10% non-response error

n = 57.04 + 5.704

n = 62.74

The preparation of wash buffer, Antigen retrieval and the whole procedure of Immunohistochemistry was done following standard protocols. The interpretation of immunohistochemistry was done as follows. Bcl-2 positivity is indicated by the cytoplasmic positivity in glandular and stromal cells. The control used for Bcl-2 cytoplasmic grading is Placenta. In the placenta the syncytiotrophoblast cells stain for grade 4 positivity (Otsuki Y 2001). Ki-67 positivity is indicated by nuclear positivity in glandular cells. The mean percentage of positive glandular cells for both Bcl-2 and Ki-67 in the functional layer of the endometrium is determined by counting 1000 cells in 10 high power fields. The high-power fields are randomly chosen as there is no standard grading system for these immunohistochemical markers. The grading system is based on the similar studies done earlier (Konno R et al.,2000, Lydia J et al.,2003, Rebekka K et al.,1998, Rekha K et al.,2005, Hurskainen R et al., et al.,2000).

Positivity for Bcl-2 and Ki-67 will be graded in to 4 grades. The BCL-2 positivity grading and KI-67 positivity grading is < 25%, 26-50%,51-75% and 76-100% for grade 1, grade 2, grade 3 and grade 4 respectively. The BCL-2 intensity grading and KI-67 intensity grading is mild, moderate, strong and very strong for grade 1, grade 2, grade 3 and grade 4 respectively.

Weighted score is the product of Positivity and Intensity. Bcl-2 stains uniformly all the glandular epithelial cells, thus number of cells showing positivity is always kept as Grade 4. In Ki-67, only cells of very strong intensity are counted as positive. So, the intensity is always kept as Grade 4 (constant). Thus, the Bcl-2 is graded mainly based on the intensity and Ki-67 is graded mainly based on the positivity and both are multiplied by 4. If negative then score is not applicable or considered as zero. Hence the maximum score obtained is 16 and minimum score obtained is 4.

RESULTS

The present study involved a total number of 65 cases of endometrial lesions. Data was entered in MS-Excel and statistical analysis was done using SPSS 23 software. Distribution of Cases were shown in **table 1**. Mean score of bcl-2 & ki-67 in cyclical endometrium and endometrial lesions were shown in **table 2**. The results were presented in descriptive statistics and appropriate test of significance with 5% level of significance and 95% confidence interval were applied. Statistical analysis was done using student t test between Bcl-2 and Ki-67 assessment and significant association (p value <0.05) was found between Bcl-2 and Ki-67 expression in proliferative endometrium, atrophic endometrium and endometrial carcinoma.(shown in **table 3**). The expression of **BCL-2** versus **KI-67**in endometrium in proliferative phase and secretory endometrium, atrophic Endometrium and disordered proliferative endometrium,simple hyperplasia without atypia and endometrial adeno carcinoma were clearly depicted in the **figures 1 to 3** respectively.

TABLE 1: DISTRIBUTION OF CASES

S.NO	ENDOMETRIAL LESIONS	SAMPLE SIZE	PERCENTAGE %
1.	Proliferative Phase	11	17%
2.	Secretory Phase	15	23%
3.	Disorderly Proliferative Phase	14	22%
4.	Hyperplasia	11	17%
5.	Atrophic Endometrium	05	7%
6.	Carcinoma	09	14%

TABLE 2: MEAN SCORE OF BCL-2 & KI-67 IN CYCLICAL ENDOMETRIUM AND ENDOMETRIAL LESIONS

S.NO	Endometrial Lesions	Samples	BCL-2/ KI-67	Negative	Score 4	Score 8	Score 12	Score 16	Mean Score
1.	Proliferative Phase	11	**BCL-2**	5	4	2	0	0	2.90
			KI-67	0	3	3	4	1	9.09
2.	Early Secretory Phase	04	**BCL-2**	0	0	0	2	2	14
			KI-67	3	1	0	0	0	1
3.	Mid Secretory Phase	05	**BCL-2**	0	2	3	0	0	6.4
			KI-67	0	5	0	0	0	4
4.	Late Secretory Phase	06	**BCL-2**	5	1	0	0	0	0.67
			KI-67	0	4	2	0	0	5.33
5	Disordered Proliferative Endometrium	14	**BCL-2**	2	2	5	2	3	8.57
			KI-67	0	6	3	4	1	8
6	Atrophic endometrium	05	**BCL-2**	1	1	0	2	1	8.8
			KI-67	3	2	0	0	0	1.6
7	SimpleHyperplasia without Atypia	11	**BCL-2**	1	1	1	4	4	11.27
			KI-67	1	3	2	3	2	8.72
8	Carcinoma	09	**BCL-2**	0	1	7	0	1	8.44
			KI-67	0	1	2	4	2	11.11

TABLE 3: STATISTICAL ANALYSIS OF BCL-2 AND KI-67 IN ENDOMETRIAL LESIONS

S.NO	ENDOMETRIAL LESIONS	SAMPLE SIZE	BCL2/KI-67	MEAN SCORE	P VALUE
1.	Proliferative Phase	11	**BCL-2**	2.90	0.0106
			KI-67	9.09	
2.	Secretory Phase	15	**BCL-2**	6.13	0.2547
			KI-67	3.73	
3.	Disorderly Proliferative Phase	14	**BCL-2**	8.57	0.4346
			KI-67	8	
4.	Hyperplasia	11	**BCL-2**	11.27	0.1068
			KI-67	8.72	
5.	Atrophic Endometrium	05	**BCL-2**	8.8	0.032
			KI-67	1.6	
6.	Carcinoma	09	**BCL-2**	8.44	0.0221
			KI-67	11.11	

Figure 1: BCL-2 VS KI-67 in Endometrium in Proliferative phase and Secretory Endometrium

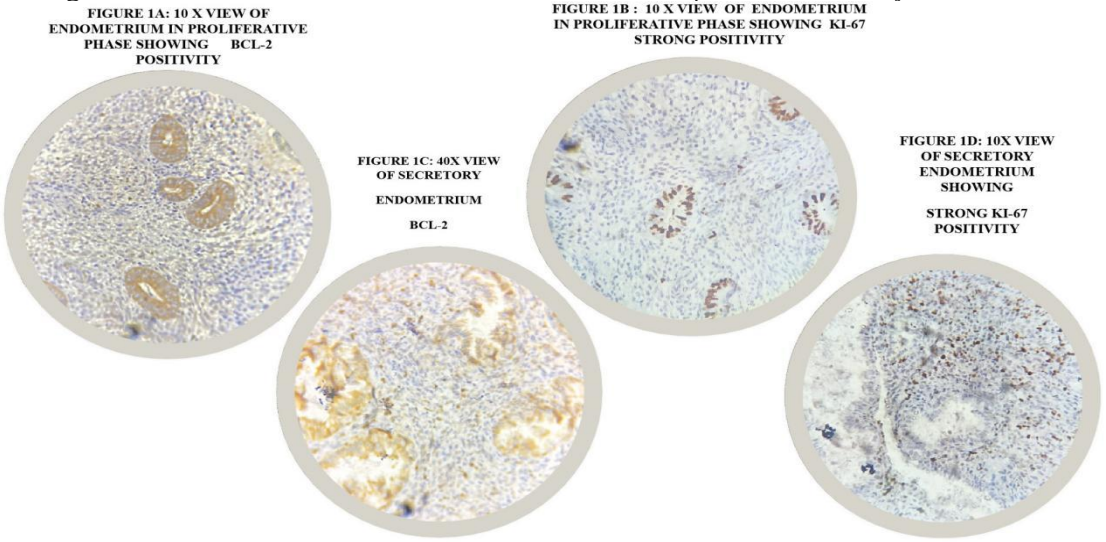


Figure 2: BCL-2 VS KI-67 in Atrophic Endometrium and Disordered Proliferative Endometrium

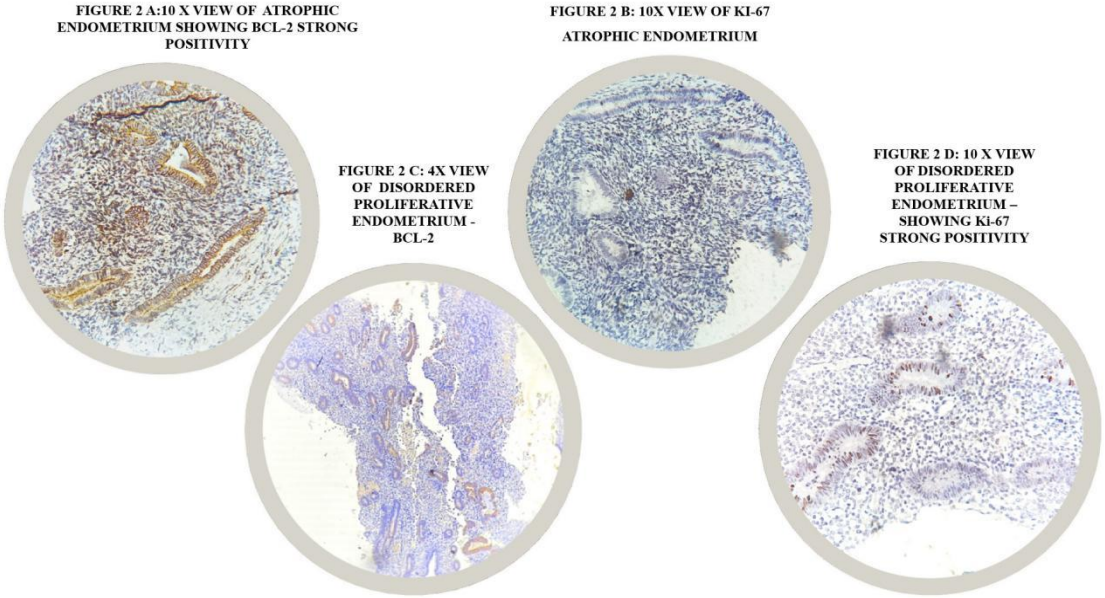
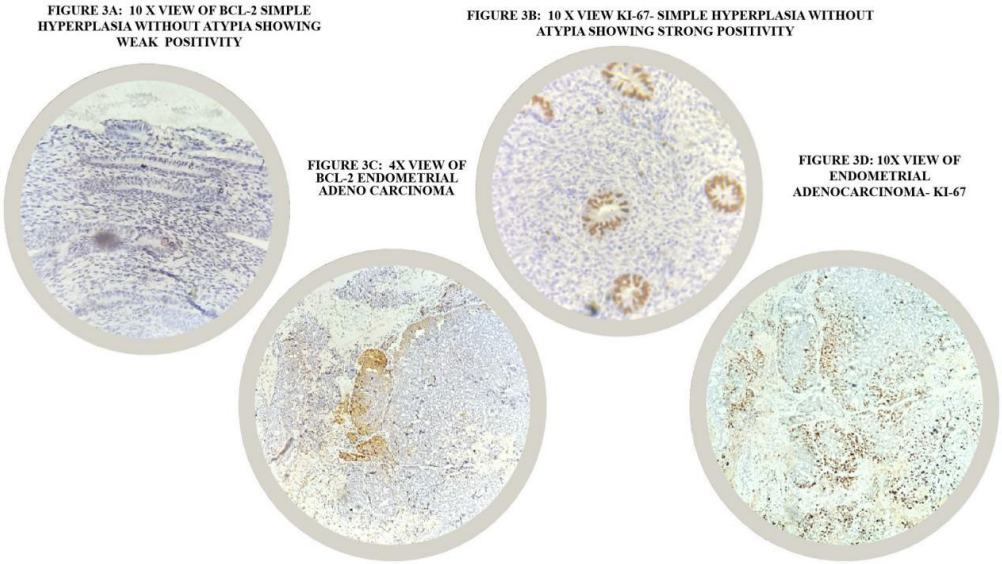


Figure 3: BCL-2 VS KI-67 in Simple Hyperplasia Without Atypia and Endometrial Adeno Carcinoma



DISCUSSION

A total of 65 endometrial samples were used in the immunohistochemical marker study. Anti-apoptotic marker Bcl-2 and proliferative marker Ki-67 were used in this study to detect apoptosis and mitosis in various endometrial lesions respectively. The endometrial lesions included proliferative endometrium, secretory endometrium, disorderly proliferative endometrium, hyperplasia, atrophic endometrium and endometrial carcinoma.

Out of 65 cases, 11 cases were proliferative endometrium (17%), 15 cases were secretory endometrium (23%), 14 cases were disorderly proliferative endometrium (17%), 11 cases were hyperplasia (17%), 5 cases were atrophic endometrium (7%) and 9 cases were endometrial carcinoma (14%). The secretory endometrium is further divided into early secretory phase, mid secretory phase and late secretory phase. Out of 11 cases of secretory phase, 4 cases were early secretory phase, 5 cases were mid secretory phase and 6 cases were late secretory phase.

Bcl-2 immunohistochemistry comprises of Bcl-2 positivity and intensity of the marker. The Bcl-2 expression mainly depends on the intensity of the marker. The number of cells showing positivity is always considered to be positive with Grade 4 positivity. Thus, intensity of the marker plays a vital role in the scoring of Bcl-2 expression. Higher Bcl-2 expression indicates decreased or absent apoptosis whereas lower expression of Bcl-2 indicates higher rate of apoptosis. In this study higher expression of Bcl-2 marker is seen in early secretory phase and lower expression of Bcl-2 marker is seen in the late secretory phase.

Ki-67 immunohistochemistry comprises of Ki-67 positivity and intensity of the marker. The Ki-67 expression mainly depends on the positivity of the marker. The intensity of the marker is always considered to be Grade 4 as the marker doesn't depend on the intensity of the stain. Thus, the number of cells showing positivity plays a vital role in the Ki-67 scoring system. Higher Ki-67 expression indicates increased mitosis whereas lower expression of Ki-67 indicates low mitosis. In this study higher expression of Ki-67 marker is seen in endometrial carcinoma cases and lower expression of Ki-67 marker is seen in the atrophic endometrium.

BCL-2 positivity was seen more in the early secretory phase with mean score of 14 followed by hyperplasia with mean score of 11.27, whereas Ki-67 positivity was seen more in the carcinoma cases with mean score of 11.11 followed by proliferative endometrium with mean scores of 9.09. Statistical analysis was done using paired t test to compare the Bcl-2 expression and Ki-67 expression in proliferative phase. Out of 11 cases of proliferative endometrium Bcl-2 positivity was seen in 55 % of the cases and Ki-67 positivity was found in 100 % of the cases with a t value of 3.1352 and a significant p value of 0.0106 (P value < 0.05 is statistically significant). This indicates that the mitotic activity and apoptotic activity is high in the proliferative phase.

This result is in concordance with similar study conducted by Mertens HJ et al in 2002 using 30 ovulatory cyclical endometrial samples showed high Ki-67 expression in the proliferative endometrium and significantly decreased expression in the secretory endometrium (Mertens HJ et al.,2002, Marisa R.Nucci et al.,2020).

Out of 15 cases of secretory endometrium Bcl-2 positivity was seen in 67 % of the cases and Ki-67 positivity was found in 87 % of the cases. Bcl-2 expression was high in the early secretory phase with mean score of 14, Bcl-2 expression decreased in the mid secretory phase with a mean score of 6.4 and Bcl-2 expression was found to be almost absent in the late secretory phase with a mean score of 0.67. Thus, indicating the onset of apoptosis in the mid secretory phase and apoptosis peaks in the late secretory phase.

Ki-67 expression was very low in the early secretory phase with a mean score of 1, Ki-67 expression was seen increased in the mid and late secretory phases of endometrium when compared to early secretory phase with mean scores of 5 and 5.33 respectively. Thus, Ki-67 expression indicates the onset of mitosis in the mid and late secretory phases which then continues to increase and peaks at the proliferative phase of endometrium.

Comparison of Bcl-2 and Ki-67 expression was done using paired sample t test. The results were not significant as the t value was 1.1876 and p value was 0.2547 (P value < 0.05 is statistically significant). Thus, in secretory phase the onset of apoptosis was in the mid secretory phase and it reached peak in the late secretory phase and antiapoptotic activity was high in the early secretory phases. Whereas the mitotic activity was less throughout the secretory phase. Mitotic activity is seen mild in the mid secretory phase and seen increased in the late secretory phase.

Out of 14 cases of Disorderly proliferative endometrium Bcl-2 positivity was seen in 85.7% of the cases and Ki-67 positivity was seen in 100% of cases with mean score of 8.57 and 8 respectively. Comparison of Bcl-2 expression and Ki-67 expression was done using paired t test in disorderly proliferative endometrium cases and no significance was found between the two with t value of 0.8062 and p value of 0.4346 (P value < 0.05 is statistically significant). There was no significance between the two immunohistochemical markers since both the Bcl-2 and Ki-67 expression was high which indicates that there is more mitosis and less apoptosis in the disorderly proliferative endometrium.

Out of 11 cases of hyperplasia, all the cases were simple hyperplasia without atypia, both Bcl-2 and Ki-67 expression was seen in 90.9 % of the cases with mean score of 11.27 and 8.72 respectively. Comparison of Bcl-2 expression and Ki-67 expression was done using paired t test in hyperplasia cases which showed no significance between the two with t value of 3.130 and p value of 0.1068 (P value < 0.05 is statistically significant). There was no significance between the two immunohistochemical markers since both the Bcl-2 and Ki-67 expression was high in hyperplasia cases, which indicates that there is more mitosis and less apoptosis in the hyperplasia cases.

Out of 5 cases of Atrophic endometrium, Bcl-2 expression was seen in 80% of the cases and Ki-67 expression was seen only in 40 % of the cases with a mean score of 8.8 and 1.6 respectively. Comparison of Bcl-2 expression and Ki-67 expression was done using paired t test in cases of Atrophic endometrium which was statistically significant with p value of 0.032. (P value < 0.05 is statistically significant). Thus, this result indicates that the antiapoptotic activity is high in the atrophic endometrium with minimal apoptosis and decreased expression of Ki-67 indicates low mitotic activity in the atrophic endometrium.

A study conducted by Havelka et al showed high expression of Ki-67 in proliferative phase and least expression was seen in atrophic endometrium which is in concordance with our study which showed ki-67 positivity of 100% in proliferative endometrium and only 40% in atrophic endometrium with mean score of 8.8 and 1.6 respectively (Havelka P et al..2005).

Out of 9 malignancy cases both Bcl-2 and Ki-67 expression was seen in 100 % of the cases with a mean score of 8.44 and 11.11 respectively. Statistical analysis was done using paired t test to compare the Bcl-2 expression and Ki-67 expression in endometrial carcinoma cases and the result obtained showed a t value of 2.8284 and p value of 0.0221 which is statistically significant. (P value < 0.05 is

statistically significant). Thus, the high expression of Ki-67 indicates increased mitosis in carcinoma cases and moderate expression of Bcl-2 indicates the presence of apoptosis in carcinoma cases in moderate amount.

A study conducted by Mahrosa MM K et al in 2008 showed high expression of Ki-67 in proliferative phases and higher expression of Ki-67 in the hyperplasia cases which is concordance with our study where the Ki-67 expression in the proliferative phase were 100% positive with a mean score of 9.09 and Ki-67 expression in the hyperplasia were 90.9% positive with a mean Ki-67 score of 8.72 (Mahrosa M.M.K et al.,2008).

A study was conducted by Morsi et al in 2000 which studied the expression of Bcl-2 and Ki-67 immunohistochemical marker expression in 107 endometrial samples The results showed high expression of Ki-67 in proliferative endometrium and low expression of both markers in secretory endometrium which is in concordance with our study where the Bcl-2 expression was low in the mid secretory phase with a mean score of 6.4 and it was almost absent in the late secretory phase with a mean score of 0.67 indicating that the apoptosis starts in the mid secretory phase and continues to increase in the late secretory phase (Morsi HM et al.,2000).

Similarly, the Ki-67 expression in the secretory endometrium was low in the early secretory phase with a mean score of 1 and the Ki-67 expression was seen slightly increased in the mid and late secretory phases of endometrium when compared to early secretory phase with mean scores of 5 and 5.33 respectively. This indicates that the mitosis is very low or absent in the early secretory phase and begins at the mid secretory phase and increases in the late secretory phase of endometrium.

A study conducted by Ambros RA et al in 2000 used Ki-67 immunohistochemical marker in 68 endometrial samples (Ambros RA. 2000). Highest Ki-67 expression was found in the proliferative phase followed by hyperplasia and the least Ki-67 expression was found in the atrophic endometrium which is in concordance with our study where the Ki-67 expression was 100% in the proliferative endometrium with a mean score of 9.09 and in hyperplasia the Ki-67 expression was 90.0% with a mean score of 8.72 and least expression of Ki-67 was found in the atrophic endometrium with a mean score of 1.6 thus, indicating the mitosis is high in the proliferative phases and in hyperplasia whereas the mitosis is very low or absent in the atrophic endometrium.

A study conducted by Maia H et al in 2004 showed that expression of Ki-67 was significantly detected during the proliferative phase compared to the secretory phase which is in concordance to our study (Maia Jr H et al.,2004). The Ki-67 expression was 100% positive in proliferative phase with a mean score of 9.09. The high expression of Ki-67 in the proliferative phase indicates mitosis in the proliferative phase of endometrial cycle.

CONCLUSION

Our study concludes that BCL2 and KI 67 shows significant association in endometrial cases. Bcl-2, an antiapoptotic marker expression was increased in hyperplasia cases and in atrophic endometrium which indicates less apoptosis. Ki-67 a marker for cell proliferation, expression was increased in proliferative phase and carcinoma cases indicating the presence of mitosis.

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