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Original Research

Radiological Correlation of Endometrial Thickness with Proliferation Marker Ki-67 in Endometrial Pathologies in Tertiary Care Hospital, Niloufer Hospital

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ABSTRACT

BACKGROUND: This study was conducted to establish a correlation between endometrial thickness and Ki-67 expression in endometrial pathologies, correlate endometrial thickness and Ki-67 expression in endometrial pathologies and evaluate the diagnostic utility of this correlation for early diagnosis of premalignant and malignant lesions, which in turn means treatment optimization.

METHODS: This was a hospital-based prospective study conducted among 100 patients who presented with abnormal uterine bleeding at the Department of Pathology, Niloufer Hospital, Red Hills, Hyderabad, over a period of two years from 2020 to 2022, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

RESULTS: Out of 100 cases, a maximum of 32% were diagnosed as endometrial hyperplasia without atypia. The least number of cases 0.3% were of endometrial carcinoma. The highest number of cases 39 (39%)-belonged to the endometrial thickness range of 11–15 mm, closely followed by the number of cases 38 (38%) with endometrial thickness between 6 and 10 mm. The mean Ki-67 LI and mean endometrial thickness for each histological entity were evaluated, and these two parameters were found to be highest in endometrial carcinoma (ET = 17.4 mm and Ki-67 LI = 38%). There was an incremental increase noted in the Ki-67 LI along the hyperplasia-to Carcinoma sequence, with Ki-67 LI being 19% in hyperplasia without atypia, 28% in atypical hyperplasia/EIN and 38% in endometrial carcinoma. Similarly, endometrial thickness also increased from 11.7 mm in hyperplasia without atypia to 14.8 mm in atypical hyperplasia or EIN and 17.4mm in endometrial carcinoma. Ki-67 LI and endometrial thickness were found to be positively correlated in cases of hyperplasia without atypia, atypical hyperplasia, carcinoma, and cystic endometrium. Our study showed a strong positive, statistically significant correlation between Ki-67 and endometrial thickness.

CONCLUSION: In endometrial pathologies, Ki-67 has established prognostic significance and predictive value, and its role as an ancillary tool along with other immunomarkers in the diagnosis and differentiation of endometrial hyperplasia and endometrial carcinoma has been documented in several studies. However, the standardisation of Ki-67 labelling index cutoff values in endometrial hyperplasia and carcinoma is yet to be established.

KEYWORDS: Endometrial Thickness, Proliferation Marker KI-67, Endometrial Pathologies.

INTRODUCTION

Ultrasonography followed by endometrial biopsy in women presenting with AUB helps in the detection of endometrial carcinoma, which is often preceded by endometrial hyperplasia.[1] Early detection of endometrial hyperplastic lesions is crucial to preventing the progression to endometrial cancer.[2,3]Ki-67 is a nuclear protein that is encoded by the MKI-67 gene. It is expressed by proliferating cells and is closely related to cellular expansion. Ki-67 acts as a nuclear antigen associated with proliferation.[4]In endometrium, it is more often detected in the proliferative phase than in the secretory phase. Evaluation and correlation of endometrial thickness and Ki-67 not only helps in early diagnosis of premalignant and malignant lesions but also screens out patients who don't need further investigations.

Aims and Objectives

- To establish a correlation between endometrial thickness and Ki-67 expression in endometrial pathologies
- To correlate endometrial thickness and Ki-67 expression in endometrial pathologies

- To evaluate the diagnostic utility of this correlation for early diagnosis of premalignant and malignant lesions, which in turn means treatment optimisation.

MATERIAL AND METHODS

This was a hospital-based prospective study conducted among 100 patients who presented with abnormal uterine bleeding at the Department of Pathology, Niloufer Hospital, Red Hills, Hyderabad, over a period of two years from 2020 to 2022, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- Adequate endometrial biopsies were received by the Department of Pathology at Niloufer Hospital.
- Total abdominal hysterectomy specimens of patients with abnormal uterine bleeding
- Patients in the reproductive age group present with abnormal uterine bleeding.
- Patients in the postmenopausal age group present with postmenopausal bleeding.

Exclusion Criteria

- Inadequate biopsy specimens for analysis
- Specimens sent in inadequate fixatives.
- Total abdominal hysterectomy specimens with a diagnosed non-endometrial cause of AUB

Statistical Methods: The correlation between Ki-67 expression and endometrial thickness was analysed using the t-test and Pearson's coefficient of correlation. A p-value of <0.05 was considered significant.
A coefficient of correlation of 0 to +1 was considered positive correlation, and 0 to -1 implied negative correlation. A value of 0 signifies no correlation between two variables.

RESULTS

Sl. No	Endometrial Lesions	010 %	11-20%	21-30%	31-40%	41-50%	51-60%	61-70%	71-80%	>80 %	Mean
1	Proliferative Phase	12	06	03	-	-	-	-	-	-	15.7
2	Secretory phase	12	02	-	-	-	-	-	-	-	7.1
3	Endometrial polyp	06	09	-	-	-	-	-	-	-	10
4	Disordered Proliferative Endometrium	03	03	-	-	-	-	-	-	-	12
5	Typical Hyperplasia	10	13	08	-	-	01	-	-	-	19
6	Atypical Hyperplasia/EIN	-	08	-	-	-	01	-	-	-	28
7	Endometrial Carcinoma	-	-	02	-	-	-	01	-	-	38

Table 1: Ki-67 Labelling Index (LI) in Various Endometrial Lesions

Ki-67 LI was noted to be the highest (38%) in endometrial carcinoma, followed by atypical hyperplasia/EIN (28%). Ki-67 LI was decreased by 7.1% in the secretory phase.

Sl. No	Endometrial Thickness Intervals	Sample size	Percentage
1	<5mm	09	09 %
2	6 – 10 mm	38	38 %
3	11 – 15 mm	39	39 %
4	16 – 20 mm	13	13 %
5	>20 mm	01	01 %

Table 2: Distribution of Cases Based on Endometrial Thickness

The maximum number of cases, 39%, belonged to the endometrial thickness interval of 11–15 mm. An almost equal number of cases, 38%, belonged to endometrial thickness between 5 and 10 mm.

Sl. No	Endometrial Lesions	<5mm	6 -10 mm	11-15mm	16- 20 mm	>20 mm	Mean
1.	Proliferative Phase	09	12	-	-	-	4.9
2.	Secretory Phase	-	08	06	-	-	9.5
3.	Endometrial Polyp	-	02	09	04	-	11.3
4.	Disordered Proliferative Endometrium	-	02	04	-	-	9.8
5.	Hyperplasia without Atypia	-	14	15	03	-	11.7
6.	Atypical Hyperplasia/EIN	-	-	04	05	-	14.8
7.	Endometrial Carcinoma	-	-	01	01	01	17.4

Table 3: Endometrial Thickness in Various Endometrial Lesions

Endometrial thickness was noted to be a maximum of 17.4 mm in cases of endometrial carcinoma, followed by cases of atypical hyperplasia or EIN of 14.8mm. It was lowest in the proliferative phase at 4.9 mm.

Sl. No.	Endometrial Lesions	Mean Ki-67 LI(40x)	ET Mean (in mm)
1	Proliferative Phase	15.7	4.9
2	Secretory Phase	7.1	9.5
3	Endometrial Polyp	10	11.3
4	Disordered Proliferative Endometrium	12	9.8
5	Hyperplasia without Atypia	19	11.7
6	Atypical Hyperplasia/EIN	28	14.8
7	Endometrial Carcinoma	38	17.4

Table 4: Comparison of Ki-67 Expression and Endometrial Thickness in Various Endometrial Lesions

Maximum Ki-67 and endometrial thickness were noted in endometrial carcinoma: Ki-67 was 38% and ET was 17.4 mm. This was followed by atypical hyperplasia (EIN -> Ki-67 (28%), and ET (14.8 mm).The p value and Pearson coefficient of 'r' are used to determine the correlation and its statistical significance between the expression of Ki-67 and endometrial thickness. 'P' value <0.05: statistically significant. >0.05 was statistically insignificant. Pearson's coefficient of correlation 'r' measures the strength of the linear relationship between two variables and has a value between -1 and +1, where r = 0 is no correlation, 0 to +1 is positive, and 0 to -1 is negative correlation.[5]

Sl. No.	Endometrial Lesions	P-Value	Coefficient of Correlation 'r'
1	Proliferative Phase	<0.0001	0.15
2	Secretory Phase	0.02	0.11
3	Endometrial Polyp	0.38	-0.12
4	Disordered Proliferative Endometrium	0.13	0.33
5	Hyperplasia without Atypia	0.0002	0.11
6	Atypical Hyperplasia/EIN	0.0005	-0.29
7	Endometrial Carcinoma	0.028	0.81

Table 5: P-Value and Pearson's Coefficient of Correlation 'r' between Ki-67 LI and Endometrial Thickness in Various Endometrial Lesions

In proliferative endometrium, the Ki-67 and endometrial thickness show statistically significant (p = <0.0001) positive correlation (r = 0.15). In cases with secretory endometrium, a statistically significant (p = 0.02) positive correlation (r = 0.112) is noted. Cases of endometrial polyps have shown a statistically insignificant (p = 0.38) weak negative correlation (r = -0.12). Cases of disordered proliferative endometrium have been statistically insignificant (p = 0.13). Positive correlation (r =0.6). Cases of typical hyperplasia demonstrated a statistically significant (p = 0.002) positive correlation (r = 0.15). Cases of atypical hyperplasia and EIN have shown a statistically significant (p = 0.005) positive correlation (r = 0.29). Cases of endometrial carcinoma have shown a statistically significant (p = 0.02) positive correlation (r = 0.81). Expression of Ki-67 and endometrial thickness showed the strongest positive correlation in cases of endometrial carcinoma (r = 0.81). A positive correlation was also noted in atypical hyperplasia/EIN, typical hyperplasia, proliferative, and secretory phases. The correlation was noted to be statistically insignificant in cases of endometrial polyps and disordered proliferative endometrium. The means of the Ki-67 labelling index and endometrial thickness were calculated, and their 'p'

and 'r' values were found to be as follows: Pearson's Coefficient of Correlation 'r' = 0.76 (positive correlation) p-value = 0.04 (statistically significant), inferring that there is a strong, statistically significant positive correlation between ki-67 and endometrial thickness.

DISCUSSION

Age Incidence: In the present study, the age range was between 32 and 71 years, with a mean age of 46 years. Out of 100 cases, 12 were postmenopausal, and 88 were in the reproductive and perimenopausal age groups.
In a study conducted by A. Ozer et al.[6] in2016, the mean age at presentation was 44.5 years. In the study conducted by Sahu M et al.[7] the mean age at presentation was 50 years. The present study correlates closely with the study by A. Ozer et al.

Clinical Presentation: In the present study, the most common presentation was abnormal uterine bleeding. 78% of cases presented with AUB, including menorrhagia, polymenorrhea, and metrorrhagia; 8% of cases presented with postmenopausal menopausal bleeding; and 14% presented with other symptoms like menometrorrhagia and pelvic mass, associated with other lesions like leiomyoma, as an incidental finding during the workup for other gynaecological conditions. These findings are in line with studies conducted by Sahu M et al. (2018) and Sur D et al.[8] (2016). In a study conducted by Sahu M et al. (2018), 80.76% of cases presented with AUB, of which menorrhagia was the most common presentation: 47 cases (39.16%), followed by polymenorrhagia: 40 cases (33.3%), and metrorrhagia: 10 cases (8.3%). Among the remaining 23 cases, 19.16% were postmenopausal bleeding. In a study conducted by Sur D et al. (2016), 89.57% of 149 cases presented with AUB (menorrhagia and metrorrhagia) and 10.43% of 17 cases presented with postmenopausal bleeding.

Histological Types of Endometrial Lesions: Endometrial pathologies present a wide spectrum of abnormalities. Endometrial pathologies have organic and inorganic etiologies. The spectrum includes inflammatory, hormonal, neoplastic, benign, and malignant conditions. In the present study, the most common histological presentation was endometrial. Hyperplasia without atypia accounts for 32% of cases. The least number of cases-03%-belong to endometrial carcinoma. The present study has a higher percentage of cases of hyperplasia without atypia when compared with the other studies. The percentage of cases of atypical hyperplasia (09%) was comparable to the study's (8.5%) results by Shrestha et al.[9] (2018). The percentage of cases falling under endometrial carcinoma was in concordance with the percentages in the studies conducted by Sujana G et al., 2020, and Shrestha et al., 2018. Out of the three above-cited studies for comparison, the present study was similar to the study conducted by Shrestha et al. (2018), wherein the percentage of cases of atypical hyperplasia, cyclical endometrium, and endometrial carcinoma were similar. In this study, we found that endometrial carcinoma had the highest mean Ki-67 LI index (38%), followed by atypical hyperplasia/EIN (28%) and hyperplasia without atypia (19%). In the cyclical endometrium, the expression of Ki-67 was higher in the proliferative phase when compared to the secretory phase. Among 32 cases of endometrial hyperplasia without atypia, the mean Ki-67 LI is 19%. In nine cases of atypical hyperplasia/EIN, the mean Ki-67 index was 28%. In five cases of endometrial carcinoma, the mean Ki-67 was calculated to be 38%. The present study relates well with the study conducted by CR Shevra et al. (2015); especially in cases of hyperplasia without atypia (27%) and atypical hyperplasia (30%). In cases of endometrial carcinoma, the mean Ki-67 index of the present study (38%) was more closely correlated with the study conducted by Nayar et al. (2017), with a mean Ki-67 index of 30.6%. A gradual and continuous increase was noted in the mean Ki-67 index as we moved through the spectrum from the proliferative phase to endometrial carcinoma. The increase was marked in hyperplasia without atypia and atypical hyperplasia, suggesting their roles as precancerous lesions in endometrial carcinogenesis. Linda B. Mora et al.observed that Ki-67-positive cells were significantly higher in endometrial carcinoma than in non-atypical or atypical endometrial hyperplasia. The study also reported that Ki-67 is higher in the proliferative phase than in the secretory phase. Shevra CR et al.noted increased expression of Ki-67 in endometrial carcinoma relative to proliferative endometrium and endometrial hyperplasia without atypia. To our knowledge, there is no standardised cutoff for the Ki-67 labelling index to differentiate between hyperplasia and arcinoma. There is a need for larger cohort studies to be carried out to evaluate the cut-off value of Ki-67 to distinguish endometrial hyperplasia without atypia, atypical hyperplasia, and endometrial carcinoma.

Distribution of Endometrial Thickness among Cases: In the present study, endometrial thickness ranged between 1 and 25 mm. The majority of cases, 39%, had endometrial thickness in the range of 11–15 mm, which was almost equal (38%) to the percentage of cases with endometrial thickness between 6 and 10 mm. The lowest percentage of cases (1%) belong to ETs above 20 mm. The endometrial thickness distribution among the cases in the present study is in concordance with the studies conducted by Sujana G et al., 2020; Shreshtha et al., 2018; and Sur D et al., 2016. The studies conducted by Shreshtha et al. (2018) and Sur D et al. (2016) show that

the majority of cases belong to the endometrial thickness range of 11–15 mm, followed closely by cases belonging to 6–10 mm. The study conducted by Sujana G et al. in 2020 demonstrated the majority of cases belonging to endometrial thickness in the 6–10 mm range, followed by the 11–15 mm range. The present study and the studies carried out by Sujana G et al.2020 and Sur D et al. (2016) reveal the lowest percentage of cases belonging to endometrial thickness above the range of 20 mm.

Endometrial Thickness in Various Endometrial Lesions: In the present study, endometrial thickness ranged between 1 and 25 mm. The highest mean endometrial thickness was noted in endometrial carcinoma (17.4 mm), followed by atypical hyperplasia (EIN) (14.8 mm). The least was noted in the proliferative phase (4.9 mm). Out of 21 cases of proliferative endometrium, nine had endometrial thickness less than 5 mm, and 12 had ET in the range of 6–10 mm. There were no cases of proliferative endometrium with an endometrial thickness greater than 10 mm.

Among 14 cases of secretory endometrium studied, eight cases had ET in the 6–10 mm range and six had ET in the 11–15 mm range. No cases were present in the ET ranges of <5mm, 16–20 mm, and >20 mm. Out of 15 cases of endometrial polyps studied, 02 were in the ET range of 6–10 mm, 09 cases were in the ET range of 11–15 mm, and 04 cases were in the ET range of 16–20 mm. No cases of endometrial polyps were noted in the range of <5 mm to >20 mm. Among the 06 cases of disordered proliferative endometrium, 02 cases had ET in the range of 6–10 mm, and 04 cases had ET in the range of 11–15 mm. No cases of disordered proliferative endometrium were seen in ET ranges of < 5mm, 16–20 mm, and > 20 mm. In 32 cases of endometrial hyperplasia without atypia studied, 14 cases were in the ET range of 6–10 mm, 15 cases in ET range of 11-15 mm and 03 cases in ET range of 16-20 mm No cases of hyperplasia without atypia were noted in the ET ranges of < 5mm and > 20 mm. Out of 09 cases of atypical hyperplasia or EIN, 4 cases had ET in the range of 11–15 mm, and 5 cases had ET in the range of 16–20 mm. No cases were noted in the ET ranges of < 5mm, 6–10 mm, and > 20 mm. Among the 03 cases of endometrial carcinoma, 01 case each was noted in the ET ranges of 11–15 mm, 16–20 mm, and >20 mm. No cases of endometrial carcinoma were found in the ET. In the present study for the ET of <5mm, all the cases (09) were of the proliferative phase. No other histological entity was noted in cases with ET <5 mm. This is similar to studies conducted by Sujana et al. (2020) and Shreshtha et al. (2018), in which all the cases of ET <5 mm belong to the proliferative phase.

ET Range of 6-10 mm: In the present study, 2% of cases of endometrial polyps and 2% of cases of disordered proliferative endometrium are noted in the ET range of 6–10 mm. Sujana et al. (2020) reported 0.2% cases of endometrial polyps and a higher incidence (11%) of disordered proliferative endometrium cases. The present study had 14% of cases in the ET range of 6 to 10 mm with histological features of endometrial hyperplasia without atypia. Shreshtha et al. (2018) reported a much lower incidence (0.9%) of endometrial hyperplasia without atypia in the ET range of 6–10 mm. No cases of hyperplasia without atypia were reported by Sujana et al. in the endometrial thickness range of 6–10 mm. No atypical hyperplasia or EIN and endometrial carcinoma were noted in the present study in the endometrial thickness between 6 and 10 mm. Similarly, no cases of atypical hyperplasia or EIN were noted in the ET range of 6–10 mm by Sujana et al.Whereas, Shreshtha et al. (2018) reported 0.9% (one case) of atypical hyperplasia in the ET range of 6–10 mm.

ET Range of 11-15 mm: In the present study, the maximum number of cases (39%) belonged to the ET range of 11–15 mm. Within this thickness range of 11–15 mm, we observed 6% of cases of secretory endometrium, 9% of cases of endometrial polyp, 4% of cases of disordered proliferative endometrium, 15% of cases of hyperplasia without atypia, 4% of cases of atypical hyperplasia/EIN, and 1% of cases of endometrial carcinoma. No cases of proliferative endometrium were noticed in this thickness range. Sujana et al.reported 0% cases of proliferative endometrium within this endometrial thickness range, which was similar to the present study. However, a higher percentage of cases (20.9%) of proliferative endometrium was reported by Shreshtha et al. in the ET range of 11–15 mm. 6% of cases of secretory endometrium were observed in the present study, with an endometrial thickness in the 11–15 mm range. 8.5% of cases were reported by Shreshtha et al.,and 12% of cases of secretory endometrium were noted by Sujana et al. In the present study, 9% of cases were endometrial polyps, and 4% were disordered proliferative endometrium. Sujana et al.reported 2% cases of endometrial polyps and a comparatively greater number (19%) of disordered proliferative endometrium cases. Within the thickness range of 11–15 mm, the present study recorded 15% cases of hyperplasia without atypia. Shreshtha et al.reported 9.5% cases, and Sujana et al. studied a relatively lower percentage (2.8% cases) of hyperplasia without atypia. In this thickness range, hyperplasia was also reported by Pillai SS et al., 2014 (3.4%) and Sur D. et al., 2016 (4.26%).
Within the endometrial thickness interval of 11–15 mm, the present study observed 4% of cases of atypical hyperplasia or EIN. Shreshtha et al.reported 0.9% (01) cases of atypical hyperplasia or EIN in this ET range, whereas no such cases were reported by Sujana et al. within this range. 1% of cases belonged to endometrial carcinoma within the ET range of 11–15 mm in the present study. Similarly, Shreshtha et al. reported 0.9% of

cases belonging to endometrial carcinoma within the ET interval of 11–15 mm. 0.4% of cases of endometrial carcinoma were noted by Sujana et al. in the same range.

ET Range of 16-20 mm: Within the ET range of 16–20 mm, the present study recorded 4% cases of endometrial polyps, 3% cases of hyperplasia without atypia, 05% cases of atypical hyperplasia/EIN, and 1% cases of endometrial carcinoma. No cases of proliferative endometrium or secretory endometrium were observed in this ET range of 16–20 mm in the present study. Likewise, Sujana et al. reported no cases of proliferative or secretory endometrium in the ET range of 16–20 mm. Shreshtha et al. reported 0.9% cases each of proliferative and secretory endometrium in this ET range. 04% cases of endometrial polyps were noted in the present study, while Sujana et al. reported 01% cases of polyps in this ET range of 16–20 mm. No cases of disordered proliferative endometrium were observed in the present study in this ET range, whereas 1.5% of cases of disordered proliferative endometrium were reported by Sujana et al. in the ET interval of 16–20 mm.
In the current study, 3% of the women had endometrial hyperplasia without atypia, with ET ranging from 16 to 20 mm. This was in concordance with the studies conducted by Sujana et al., 2020, and Shreshtha et al., 2018. Sujana et al. recorded 2.8% cases, and Shreshtha et al. reported 1.9% cases of hyperplasia without atypia in the ET range of 16–20 mm. 5% of cases of atypical hyperplasia or EIN were recorded in the present study, with endometrial thickness falling in the range of 16–20 mm. Shreshtha et al. reported almost the same percentage of 5.8% cases, and Sujana et al. reported a lower incidence of 0.4% of atypical hyperplasia or EIN cases in the ET range of 16–20 mm. The present study had 1% of cases of endometrial carcinoma within the ET interval of 16–20 mm. Similar findings were observed by Sujana et al., 2020, and Shreshtha et al., 2018. Shreshtha et al. reported 1.8% cases of endometrial carcinoma, and Sujana et al. reported 2% cases of endometrial carcinoma with endometrial thickness between 16 and 20 mm.

ET of > 20 mm: In the present study, endometrial thickness >20 mm was noted only in 1% (01) of cases with the histological appearance of endometrial carcinoma. No other histomorphological entities were noted in the present study with ET > 20 mm. Sujana et al.recorded 0.2% (01) cases, and Shreshtha et al. recorded 9% (01) cases of endometrial hyperplasia without atypia with endometrial thickness above 20 mm. No cases of hyperplasia without atypia were found in the present study. The present study and the study conducted by Sujana et al. recorded no cases of atypical hyperplasia or EIN with ET greater than 20 mm. Shreshtha et al. reported 0.9% (01) cases of this histolopathological entity with ET higher than 20 mm. 01% (01) cases of endometrial carcinoma were observed in the present study with ET greater than 20 mm. Likewise, 1.8% (07) cases were reported by Sujana et al. with ET >20 mm. No cases of endometrial carcinoma were observed by Shreshtha et al. with ET higher than 20 mm. With the increase in endometrial thickness from <5mm to >20mm, the incidence of endometrial hyperplasia without atypia, atypical hyperplasia/EIN and endometrial carcinoma increased. A similar trend of increased incidence of hyperplasia and carcinoma, along with an increase in endometrial thickness, was observed in other studies conducted by Sujana et al., Shreshtha et al.,Pillai SS et al., Sur D et al.,and Getpook C et al.[10]

Relationship between Ki-67 and Endometrial Thickness: Endometrial carcinoma is usually the end result of the histological spectrum through hyperplasia without atypia and atypical hyperplasia or EIN. Hyperplasia, in some cases, may be preceded by disordered proliferative endometrium. It is known that these stages have the potential to evolve into endometrial carcinoma, making them premalignant lesions. The present study was aimed at early detection of these lesions and diagnostic improvement in regards to this spectrum. The hyperplasia-carcinoma continuum is usually associated with the unopposed oestrogen effect. Hence, oestrogen is considered an endometrial carcinogen. The molecular culprits in the causation of endometrial carcinoma are the p53 mutation, loss of PTEN function, POLE mutation, and microsatellite instability. In our study, the mean Ki-67 LI was found to be raised by 28% in atypical hyperplasia/EIN and 38% in endometrial carcinoma. The study suggests the possible use of Ki-67 as an informative biomarker for the identification of these precancerous lesions. In the present study, mean endometrial thickness was found to be maximum (17.4 mm) in endometrial carcinoma, followed by atypical hyperplasia/EIN. As the endometrial thickness increased from <5 mm to >20 mm, the incidence of hyperplasia and endometrial carcinoma increased. The study conducted by Getpook C et al.concluded that endometrial thickness of 8 mm or less is likely to be associated with malignant pathology in perimenopausal women with abnormal uterine bleeding. In postmenopausal women, an ET of 4 mm or less was considered normal; if it is more than 4 mm, the chances of abnormalities like hyperplasia and carcinoma are higher. The upper limit for normal endometrial thickness remains controversial, but most studies have reported an ET of 8 mm as the abnormal cutoff value, necessitating further investigations. In the present study, the mean Ki-67 LI and mean endometrial thickness were calculated, and it was observed that there exists a strong positive correlation ($r = 0.76$) between the two, which is statistically significant ($p = 0.04$).The study suggests that the Ki-67 LI could be higher in cases where the endometrial thickness was above the cutoff value of 8 mm, and the

number of cases of hyperplasia and cancer was also high. Hence, these patients need to be subjected to further investigations and are thus amenable to early surgical therapy when required. PTEN to confirm or rule out endometrial carcinoma in doubtful cases. Linda B. Mora et al.observed that Ki-67-positive cells were significantly higher in endometrial carcinoma than in non-atypical or atypical endometrial hyperplasia. Shevra CR et al.noted increased expression of Ki-67 in endometrial carcinoma relative to proliferative endometrium and endometrial hyperplasia. Boruban MC et al.[11] in their study that the p53 gene mutation was not found in endometrial hyperplasia but was seen in 20% of cases of endometrial carcinoma. Mutation of PTEN was present in 83% of endometrial carcinoma cases, making it the most frequent early molecular genetic alteration in endometrial carcinoma. Masjeed N et al. observed higher ER and PR expression in endometrial hyperplasia without atypia than in atypical hyperplasia and endometrial carcinoma. Using immunomarkers like ER, PR, p53, and PTEN, along with Ki-67, facilitates the differentiation of endometrial hyperplasia, atypical hyperplasia, and endometrial carcinoma. It serves as an adjunct tool for differentiating endometrial hyperplasia from endometrial carcinoma.

Ki-67 is increasingly being used in endometrial carcinoma as a primary outcome measure. Unlike in breast cancer, there are no guidelines standardizing its measurement and its clinical relevance as a response biomarker is undetermined. It is therefore imperative that Ki-67 scoring protocols are optimized and its association with patient survival rigorously evaluated in order to clinically interpret the results of these studies.[12] In the present time, Ki-67 has more prognostic value and serves as an ancillary tool in the diagnosis of endometrial pathologies. Sidonia et al.[13] observed that the highest Ki-67 index was in poorly differentiated carcinomas, and a high Ki-67 index was associated with myometrial invasion. Salvensen HB et al.[14] found that survival for endometrial carcinoma is significantly related to Ki-67 expression, low survival rates were present in the category of tumours with the highest Ki-67 values.

CONCLUSION

Endometrial carcinoma is the sixth most common cancer in women worldwide. This study was conducted with the objective of early detection of endometrial carcinoma and its precursor lesions by determining the correlation between Ki-67 and endometrial thickness. In the present study, mean Ki-67 LI was found to be highest in endometrial carcinoma, followed by atypical hyperplasia. The mean endometrial thickness was also noted to be highest in endometrial carcinoma, followed by atypical hyperplasia. There was an increase in the Ki-67 LI from hyperplasia without atypia to atypical hyperplasia/EIN and endometrial carcinoma, with Ki-67 LI being 19% in hyperplasia without atypia, 28% in atypical hyperplasia/EIN and 38% in endometrial carcinoma. Similarly, endometrial thickness also increased from 11.7 mm in hyperplasia without atypia to 14.8 mm in atypical hyperplasia or EIN and 17.4mm in endometrial carcinoma. In cyclical endometrium, a higher Ki-67 LI was seen in the proliferative phase in comparison with the secretory phase. The present study shows a statistically significant positive correlation between the Ki67 index and endometrial thickness. This correlation establishes its utility in the early diagnosis of endometrial carcinoma and its precursor lesions, which in turn accelerates the treatment. The present study certifies the diagnostic utility of correlating Ki-67 index and endometrial thickness for therapeutic and prognostic benefits in endometrial carcinoma and endometrial hyperplasia. In endometrial pathologies, Ki-67 has established prognostic significance and predictive value, and its role as an ancillary tool along with other immunomarkers in the diagnosis and differentiation of endometrial hyperplasia and endometrial carcinoma has been documented in several studies. However, the standardisation of Ki-67 labelling index cutoff values in endometrial hyperplasia and carcinoma is yet to be established.

REFERENCES

1. Wankhade A, Vagha S, Shukla S, Bhake A, Laishram S, Agrawal D, et al. To correlate histopathological changes and transvaginal sonography findings in the endometrium of patients with abnormal uterine bleeding. J Datta Meghe Inst Med Sci Univ 2019;14:11-5.
2. Shajitha S, Sangeereni M, Mallika A. The study of endometrial thickness by transvaginal USG with its histopathology correlation in abnormal uterine bleeding. International Journal Of Current Medical And Pharmaceutical Research 2017;3(10):2487-90.
3. GeethaLakshmi S. Ultrasonographic measurement of endometrial thickness and histopathological diagnosis of endometrial hyperplasia in abnormal uterine bleeding -a correlative study. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 2018;17(10):14-9.
4. Ghalib Farhood R Al-Humairi IAA. Immunohistochemical study of Ki-67 in hyperplastic and endometrium carcinoma: a comparative study. Arch Razi Inst 2022;77(1):229-34.
5. Sedgwick P. Pearson's coefficient of correlation. BMJ Clinical Research 2012;345:4483
6. Ozer A, Ozer S, Kanat-Pektas M. Correlation between transvaginal ultrasound measured endometrial thickness and histopathological findings in Turkish women with abnormal uterine bleeding. J Obstet Gynaecol Res 2016;42:(5):573-8.

7. Sahu M, Das S, Padmavati VM, Panigrahi PK. Correlation of endometrial thickness, hysteroscopic finding and histopathological diagnosis in patients with abnormal uterine bleeding. Annals of International Medical and Dental Research 2018;4(6):9-13.
8. Sur D, Chakravorty R. Correlation of endometrial thickness and histopathology in women with abnormal uterine bleeding. Journal of Reproductive System and Sexual Disorders 2016;5(4):192.
9. Shrestha P, Shrestha S, Mahato V. Endometrial study by Ultrasonography and its correlation with histopathology in abnormal uterine bleeding. Asian Journal of Medical Sciences 2018;9(2):31-5.
10. Getpook C, Wattanakumtornkul S. Endometrial thickness screening inpremenopausal women with abnormal uterine bleeding. Journal of Obstetrics and Gynaecology Research 2006;32(6):588-92.
11. Boruban MC, Altundag K Kilic GS, Blankstein J. From Endometrial Hyperplasia to endometrial cancer: insight into the biology and possible medical preventive measures. European Journal of Cancer Prevention 2008;17(2):133-8.
12. Kitson S, Sivalingam VN, Bolton J, McVey R, Nickkho-Amiry M, Powell ME, et al. Ki-67 in endometrial cancer: scoring optimization and prognostic relevance for window studies. Mod Pathol 2017;30(3):459-68.
13. Stoian SC, Simionescu C, Mărgăritescu C, Stepan A, Nurciu M. Endometrial Carcinoma: correlation between ER, PR, Ki-67 status and histopathological prognostic parameters. Rom J Morphol Embyol 2011;52 (2):631-6.
14. Salvesen HB, Iversen OE, Akslen LA. Prognostic significance of angiogenesis and Ki-67, p53, and p21 expression: a population-based endometrial carcinoma study. Journal of Clinical Oncology 1999;17(5):1382-90.