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Comparison of Endometrial Changes in Uterine Leiomyoma and Adenomyosis of Uterus with Correlation of Serum Estradiol and Progesterone Levels

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Abstract
Background: *Both leiomyoma and adenomyosis are commonly encountered gynecological pathologies. It is a well-established fact that hyperestrogenic state is associated with growth of leiomyoma but the exact etiology of adenomyosis is unknown. Adenomyosis is also thought to be an estrogen dependent disease. Similarly, it has also been found that progesterone receptors are increased in leiomyomas whereasa decreased responsiveness of the ectopic endometrium to progesterone has been found in adenomyosis. Thus these two hormones are intricately related to leiomyoma and adenomyosis.*
Aims: *The aim of this study is to note the changes in endometrium that can be found in the respective cases of uterine leiomyoma and adenomyosis of uterus.*
Materials and Methods: *The study was conducted over a period of 12 months included 73 cases of leiomyoma and 73 cases of adenomyosis. Serum estradiol and progesterone levels of all the patients were measured by chemiluminescence immunoassay.*
Results: *In leiomyoma, inactive basal endometrium was the most common finding 36/73 (49.31%) and in adenomyosis simple hyperplasia of endometrium was found in majority 30/73 (41.09%). However, both estradiol and progesterone levels in leiomyoma and adenomyosis were mostly within the normal range.*
Conclusion: *Though both leiomyoma and adenomyosis are associated with a hyper estrogenic state, leiomyoma had inactive basal endometrium while adenomyosis had hyperplasia. Adenomyosis was also found to be associated with other pathologies like endometrial carcinoma, complex hyperplasia. Hence, in adenomyosis other associated pathologies should be looked for.* .
Keywords: *Inactive basal endometrium, endometrial hyperplasia, estradiol, progesterone.*

Introduction

The endometrium is uniquely endowed throughout the female reproductive lifespan with complex regular cycle of periodic proliferations, differentiation, breakdown and regeneration. Before puberty the endometrial tissue is inactive, it is composed of tubular glands, a dense fibroblastic stroma and thin blood vessels. In normal menstrual cycles, the menstrual shedding

is followed by endometrial proliferation under estrogenic stimulation. After ovulation, the secretion of progesterone inhibits the proliferative activity of the endometrium and induces a complex secretory activity within the endometrium.[1]During climacteric, ovarian activity declines. Initially, ovulation fails, no corpus luteum forms, and no progesterone is secreted by the ovary.[2,3] Hyperplasias of the endometrium can develop in woman at any age with unopposed estrogen. Hyperplasia with cytologic atypia represents the greatest risk for progression to endometrial carcinoma and the presence of concomitant carcinoma in women with endometrialhyperplasia.[4]

Uterine leiomyomas are benign uterine tumors of unknown etiology. These kinds of lesions seem to arise from myometrial transformation. The majority of these estrogen dependent uterine neoplasms afflict mostly women of reproductive age group and 80% of them suffer from this during their whole lifetime[5]. Uterine leiomyoma growth is strictly related to estrogens and their receptors. Estrogens may exert growth stimulatory effects on leiomyomas intermediated by cytokines, growth factors or apoptosis factors[6]. Progesterone interacts with its receptors PR-A and PR-B playing a key role in leiomyoma biologies. Progesterone can stimulate leiomyoma cell growth and survival through upregulating Bcl-2 protein expression and downregulating TNF-α expression. [7,8]High estrogen level is associated with an increased risk of fibroid in midlife women (42-57 years) who never reported of fibroids before. Conversely the risk of recurrent fibroid was mitigated in women with high E_2.[9]

Adenomyosis is a distinct pathologic entity, not physiologic or neoplastic, characterized by heterotopic endometrium in hyperplastic endometrium.[10] Adenomyosis isalso an estrogen dependent disease caused by a downward extension of the endometrium into the uterine myometrium. Endometrium from women without endometrial disorders were used as controls. In estrogen receptor positive cultured (Ishikawa) endometrial cells, estrogen induced a morphological change to fibroblast like phenotype, a shift from epithelial- mesenchymal transition[11]. Adenomyotic lesions produce significant quantities of progesterone and contain strikingly lower levels of PR[12,13]. The protective role of progesterone in endometrial cancer is not completely applicable in adenomyosis, since adenomyosis is not a pure epithelial proliferation but rather an increased inflammation and cell survival due to diminished apoptosis or differentiation[14, 15]. High estrogen concentration and impaired immune related growth control in ectopic endometrium may be necessary for maintenance of adenomyosis[16].

Different literatures reviewed, had revealed unopposed hyperestrogenic state is the most common cause endometrial hyperplasia[4]. It is a well-known fact that hyperestrogenic state is one of the most important factors responsible for the growth of leiomyoma. Hyperestrogenic states are also associated with endometrial hyperplasia, which is a precursor lesion of endometrial adenocarcinoma, particularly when associated with nuclear atypia. Adenomyosis is also frequently associated with endometrial hyperplasia, possibly because of its association with hyperestrogenic states. But so far no literature has compared the endometrial findings in adenomyosis and leiomyoma.

Considering the postulate of hyperestrogenic state in both adenomyosis and leiomyoma, the endometrial changes may be seen in both condition and therefore can be assessed on that basis, to find out the possible causative association between adenomyosis, leiomyoma and endometrial hyperplasia or any other specific changes in endometrium.

Similarly, it has also been found that progesterone receptors are increased in leiomyomas whereas decreased PR in the ectopic endometrium has been found in adenomyosis.

So, the levels of these two hormones that is estrogen and progesterone can be estimated in the serum of the respective patients to assess their

correlation in the pathogenesis of both these conditions.

As estradiol is the most potent estrogen present during the reproductive age group. Hence, here the level of estradiol is measured.

Materials and Methods

The study was conducted over a period of 12 months from June 2016 to July 2017.

Hysterectomy specimens of patients diagnosed with leiomyoma and adenomyosis with or without salphingo- oophorectomy were sent from the Operation Theatre of Gynecology and Obstetrics Department to the Pathology Department along with duly filled up consent and case record form. Study group comprised of 73 cases of adenomyosis and 73 cases of leiomyoma. The blood of the patients were collected and send to the Department of Biochemistry for estradiol and progesterone measurement.

After gross examination, sections from the Endomyometrium at 1cm interval were taken and processed. Haematoxylin and eosin staining were done on the slides that were prepared from the sections.

Results

In leiomyoma 63.01% of patients and in adenomyosis 53.42% belonged to the age group of 41-45 years. The most common presenting complain in both the pathologies was menorrhagia (57.53% in leiomyoma, 75.34% in adenomyosis). In both cases, majority of the patients had their menarche in the age group of 12-14 years (87.67% in leiomyoma, 73.97% in adenomyosis).

Table 1: Endometrial histopathological findings in leiomyoma

Histopathology	No of patients	%
Inactive basal Endometrium	36	49.31
Simple endometrial hyperplasia	1	1.36
Secretory endometrium	15	20.54
Proliferative endometrium	21	28.76
Total	73	100

Table 2: Endometrial histopathological findings in adenomyosis

Histopathology	No of patients	%
Simple endometrial hyperplasia	30	41.09
Secretory endometrium	14	19.17
Proliferative endometrium	25	34.24
Endometrial hyperplasia with atypia	2	2.73
Endometrial carcinoma	2	2.73
Total	73	100

Table 3: Associated endometrial pathologies in leiomyoma and adenomyosis

Associated pathologies	Adenomyosis& % of total	Leiomyoma& % of total	Total& %
Simple endometrial hyperplasia	30 (96.77%)	1 (3.22%)	31 (100%)
Endometrial hyperplasia with atypia	2 (100%)	0 (0%)	2 (100%)
Endometrial carcinoma	2 (100%)	0 (0%)	2 (100%)
Inactive basal endometrium	0 (0%)	36 (100%)	36 (100%)

Thus we see that maximum number of pathologies like endometrial hyperplasia with atypia, endometrial carcinoma and simple endometrial hyperplasia are associated with adenomyosis. While only inactive basal endometrium is found in leiomyoma.

Each patient's estradiol level was assessed on the basis of the following range-

Follicular phase- 15 to 112 pg/ml

Preovulatory phase- 136 to 251 pg/ml

Luteal phase- 48 to 172 pg/ml

Each patient's progesterone was assessed on the basis of the following range-

Follicular phase- 0.4 to 2.3 ng/ml

Luteal phase- 1.2 to 18.8 ng/ml

Table 4: Estradiol and progesterone levels in adenomyosis

Estradiol	No of patients & %	Progesterone	No of patients & %
Low	9 (12.32%)	Low	9 (12.32%)
Normal	42 (57.53%)	Normal	59 (80.82%)
High	22 (30.13%)	High	5 (6.84%)
Total	73 (100%)	Total	73 (100%)

Table 5: Estradiol and progesterone levels in leiomyoma

Estradiol	No of patients & %	Progesterone	No of patients & %
Low	23 (31.50%)	Low	14 (19.17%)
Normal	39 (53.42%)	Normal	52 (71.23%)
High	11 (15.06%)	High	7 (9.58%)
Total	73 (100%)	Total	73 (100%)

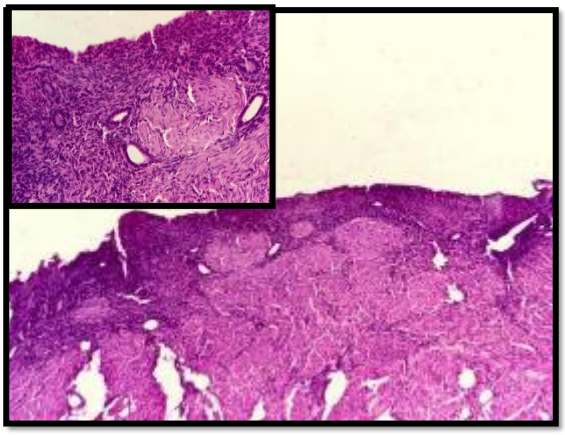

Figure 1: Inactive basal endometrium (H&E, 100x); inset at 400x.

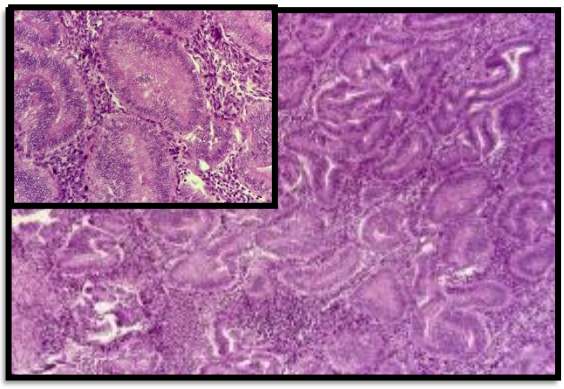

Figure 2: Simple endometrial hyperplasia (H&E, 100x); inset at 400x.

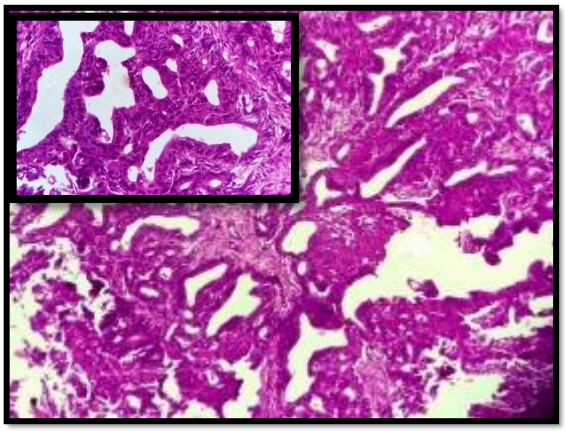

Figure 3: Complex atypical endometrial hyperplasia (H&E, 100x); inset at 400x.

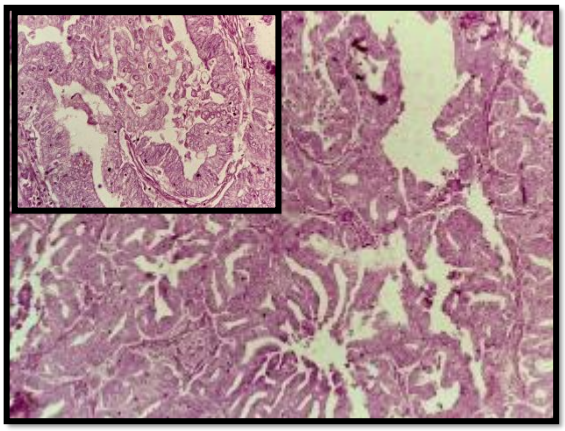

Figure 4: Endometrial adenocarcinoma (H&E, 100x); inset at 400x.

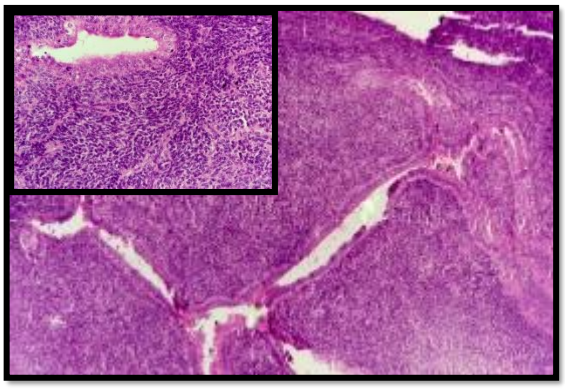

Figure 5: Adenomyosis (H&E, 100x); inset at 400x

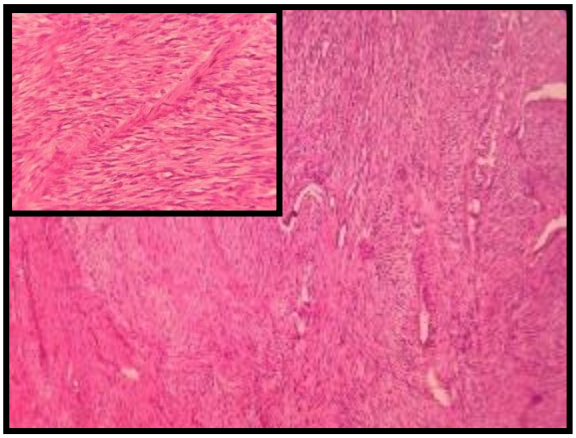

Figure 6: Leiomyoma (H&E, 100x); inset at 400x

Discussion

In the study conducted by Deligdish, Lowenthal M[17] in the year 1970, they found that the endometrial changes found in leiomyomas were distortion, dilatation and atrophy of the endometrial glands lying in close proximity of myomas. They thought hormonal factors and mechanical factors were responsible. Similarly, Mannem, Kumar H, Munikrishna M[18] concluded that leiomyoma is a steroid dependant tumor where a mixed finding of proliferative phase, hyperplasia, and endometrial atrophy can be found. This corroborated with the study, as we found a wide variety of endometrial changes ranging from secretory endometrium, proliferative endometrium, and endometrial hyperplasia to inactive basal endometrium (atrophic).

Ferenczy A[16] in the year 1998 postulated that adenomyosis was triggered by relatively high estrogen concentration and impaired immune related growth control. Hence, smooth muscle hypertrophy and hyperplasia along with endometrial proliferation are quite common in adenomyosis hyperplasia. In our study simple endometrial hyperplasia was the most common finding as expected.

Ferenczy A[16] has also stated that adenomyosis is mostly associated with other endometrial pathologies like endometrial polyps (2.3%), endometrial hyperplasia (7%), atypical endometrial hyperplasia (3.5%), adenocarcinoma (1.4%). Whereas, Deligdish, Lowenthal M[17] had stated that leiomyoma is associated with the pathology of endometrial atrophy most commonly. We found endometrial hyperplasia, atypical endometrial hyperplasia, and endometrial adenocarcinoma in the endometrium of patients with adenomyosis and leiomyoma patients had atrophic endometrium

The study conducted by Chen, Wang, Yen[18] et al in the year 2014 showed that 30 adenomyosis patients and 30 controls did not have much difference in the serum levels of estradiol and progesterone as we found in our study.

In another study conducted by Englund, Blanck, Gustavson[19] in the year 1998 the concentration of serum estradiol and progesterone level in 14 leiomyoma patients (55.55%) were within normal range thus echoing our findings as well.

Conclusion

To conclude, we can say that on comparison of endometrial changes in adenomyosis and leiomyoma, we found that in spite of having hyperestrogenic state as a factor for growth, leiomyoma shows inactive basal endometrium. Adenomyosis is most frequently associated with other endometrial pathologies.

We also concluded that the serum level of estradiol and progesterone in most cases were normal. Hence, the hyperestrogenic state is probably a localized phenomenon within the uterus.

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