Endometrial Histological Findings in Infertile Women

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Original Article

Abstract
Background and Objective: Infertility is a global health problem and in Pakistan frequency of subfertility is 21.9%. The fact that cyclical histological changes in the endometrium correlate with fluctuating biorhythms of various hormone levels enables histological appearance of the endometrium to be a reliable parameter to evaluate the cause of infertility.

Objective: To discern the histological patterns of endometrium in infertile women.

Materials and Methods: This study was carried out at the clinic of one of the authors. The study included 120 consecutive cases of infertile women seeking Assisted Reproductive Treatment. D & C was performed to obtain the endometrial biopsy. The biopsy specimen was then fixed, processed and sectioned. Haematoxylin and Eosin staining was performed. Histological sections were examined under the microscope for evaluation of morphological features. The results were analyzed and percentages calculated.

Result: In the present study majority of patients (46.6%) belonged to 26-30 years age group. Amongst the morphological patterns observed, the percentage of cases in secretory phase was the maximum. There were 17 (14%) cases of cystic hyperplasia and the feature of intraluminal tufting was noted in 65 (54%) cases. Additionally, there were 4 (3.3%) cases of non specific endometritis and 1 (0.8%) case of tuberculous endometritis. In majority of the cases (46.7%) there was sporadic lymphocytic infiltration.

Conclusion: Endometrial biopsy give information about hormone response of endometrium as well as the local factors of endometrium concerning non-specific and specific infections, tuberculous endometritis, hyperplasias and anovulatory cycle.

Key Words: Endometrium; infertility

Introduction
Infertility which refers to inability to achieve conception even after one year of unprotected coitus by a couple, is a global health problem, as it affects about 80 million people world wide.1 According to a survey by WHO the frequency of subfertility in Pakistan is 21.9% 2 and 22% of the gynaecological consultation in Pakistan are regarding the treatment of infertility.3 Infertility may be primary, when a couple has never been able to conceive or secondary when there is difficulty conceiving after already having conceived.4 The fact that cyclical morphological changes in the endometrium correlate with fluctuating biorhythms of various hormone levels enables histological appearance of the endometrium to be a reliable parameter to evaluate the cause of infertility.5,6

Morphologically, the menstrual cycle is triphasic. During the proliferative phase the endometrium continues to develop and becomes thickened under the influence of estrogens secreted by the developing ovarian follicles. This phase is further categorized into early, mid and late proliferative phases. In secretory phase, glands become tortuous, their lumens become dilated, and there is edema in the lamina propria. During the menstrual phase the endometrium undergoes degeneration and shedding. This shedding is mainly composed of fragments of uterine glands, blood clots and disintegrated stroma.7 The dating of the endometrium by its histological appearance is helpful clinically to document ovulation, assess hormonal status and determine causes of endometrial bleeding and infertility.7 Infertility is either anovulatory (absence of ovulation) or ovulatory (with normal ovulation). Secretory phase endometrium in premenstrual biopsies indicates that the ovulation has occurred and therefore the cause of infertility is other than ovulation. But all those cases in proliferative phase in premenstrual biopsies indicate anovulation and this is a major cause of infertility. Main causes of anovulatory cycles are polycystic ovary syndrome, ovarian neoplasms, enzyme deficiency, gonadal dysgenesis, autoimmune reactions, luteinized unruptured follicle syndrome and depending upon the amount of estrogen secreted endometrium is resting, atrophic, irregularly proliferative or hyperplastic. In ovulatory infertility absolute or deficient progesterone deficiency may result in deficient secretory phase with delayed maturation of glands and stroma.8

Amongst various causes of infertility related to endometrium, endometrial hyperplasia is characterized by the overgrowth or thickening of the endometrial lining due to high levels of estrogen and insufficient levels of progesterone due to anovulation. Endometritis is another cause of infertility, and is due to pelvic infection or sexually transmitted diseases.8 In acute endometritis there is presence of neutrophils while in chronic endometritis there is presence of plasma cells in the endometrial stroma.9,10 Other
than neutrophils and plasma cells, it is said that endometrial lymphocytes play a critical role in endometrial receptivity.\textsuperscript{11} Tuberculosis of the female genital tract is a fairly common extrapulmonary manifestation of the disease, and clinically infertility is the most common presentation.\textsuperscript{12} Tuberculous endometritis histologically shows non-caseating granulomas composed of epithelioid cells, Langhan giant cells and peripheral lymphocytes.\textsuperscript{13}

The evaluation of premenstrual endometrial biopsies is useful for the identification of anovulatory cycles, hyperplasias and endometritis especially tuberculous endometritis. It is an important investigation because it can be easily done in developing countries like Pakistan, where complex immunological and hormone assay procedures are not easily available and it is also easily affordable.

The present study aimed at evaluating the histological patterns of endometrium in infertile women in an attempt to establish the cause of infertility.

**Materials and Methods**

The present cross-sectional study was carried out at the clinic of one of the authors. The study included 120 consecutive cases of infertile women. In all the cases it was ensured that there was no male factor and complaints of infertility were more than one year duration. Clinical history from each patient was recorded on a performa and details regarding her age, menstrual cycle, last menstrual period, age at marriage and obstetric history were noted. D & C was performed and specimens obtained were fixed in 10% formalin fixative and processed routinely. From each biopsy 5-6 micron sections were cut and stained using haematoxylin and eosin stains.

The stained histological sections were viewed under the microscope for the evaluation of morphological features, such as secretory phase, proliferative phase, hyperplasias, intraluminal tufting, non specific endometritis, tuberculous endometritis, and abnormal lymphocytic infiltrate. Lymphocytic infiltration in stroma was noted and categorized as sporadic, aggregates and lymphoid follicles. In the statistical analysis, percentages (frequencies) of various parameters were calculated.

**Results**

In a total of 120 endometrial biopsies, the age ranged from 21 to 37 years, with a mean age of 29 years. Majority of patients belonged to 26-30 years age group. The data pertaining to age distribution in different infertile patients is given in Fig 1

As shown in table 1, amongst the morphological patterns observed, the percentage of cases in secretory phase was the maximum.

Among secretory phase there were 45 (37.5%) cases of early, 17 (14%) of mid and 6 (5%) of late secretory phase. One fourth of the cases were of proliferative (anovulatory) phase endometrium. Some cases were of cystic hyperplasias and the feature of intraluminal tufting was noted in 65 (54%) cases. Additionally, there were few cases of non specific endometritis and tuberculous endometritis. Only those cases in which plasma cells were identified were categorized into chronic non specific endometritis.

In majority of the cases there was sporadic lymphocytic infiltration. Table 2 shows the distribution of lymphocytic infiltrate in endometrium of infertile patients.

**Table 1: Various histological patterns in endometrium of infertile women (n 120)**

<table>
<thead>
<tr>
<th>Type of endometrium</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Secretory phase</td>
<td>45 (37.5)</td>
</tr>
<tr>
<td>Mid Secretory phase</td>
<td>17 (14.1)</td>
</tr>
<tr>
<td>Late Secretory phase</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Proliferative (anovulatory) phase</td>
<td>30 (25)</td>
</tr>
<tr>
<td>Simple cystic hyperplasia</td>
<td>17 (14.1)</td>
</tr>
<tr>
<td>Non specific endometritis</td>
<td>4 (3.33)</td>
</tr>
<tr>
<td>Tuberculous endometritis</td>
<td>1 (0.83)</td>
</tr>
</tbody>
</table>

**Table 2: Distribution of lymphocytic infiltrate in endometrium of infertile patients (n 120)**

<table>
<thead>
<tr>
<th>Lymphocytic infiltration in stroma</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>56 (46.7)</td>
</tr>
<tr>
<td>Aggregates</td>
<td>40 (33.3)</td>
</tr>
<tr>
<td>Lymphoid follicles</td>
<td>24 (20)</td>
</tr>
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</table>

**Fig 1: Age distribution among infertility patients in percentage (n 120)**
Discussion

The prevalence of infertility has been fairly constant over the past years but the demand for assisted reproductive techniques has increased with time. Infertility can lead to severe psychological morbidity. Many authors have stressed that endometrial biopsy is a safe technique and it provides an evidence of normal endometrial development. Disturbance of menstrual cycles can lead to infertility by altering the histological appearance of endometrium due to which blastocyst cannot implant and this leads to infertility. Endometrial biopsies are being studied for infertility as a routine investigation for many decades. The morphological patterns observed in this study were compared with the results of other studies which were similar to our findings. Girish et al (2011) studied 90 endometrial biopsies in which most of the cases were of secretory phase (56.7%). Anovulatory cycles were observed in 32.3%, simple cystic hyperplasias in 5.5%, non specific endometritis in 2.2%, and tuberculous endometritis in 2.2% cases. The results are similar to our study in which secretory phase endometrial cases were 56.6%, anovulatory cycles 25%, simple cystic hyperplasias 14%, non specific endometritis 3.3% and tuberculous endometritis 0.83%.

In a wide ranged series of endometrial biopsies of infertile couples in Turkish population most of the cases were in the age group range of 26-35, similar to our study. In this study most cases were of secretory endometrium (37%) and 20.95% cases were of proliferative phase (anovulatory). In a study by Zawar et al there were 200 endometrial biopsies of infertile females. Anovulatory cycles were in 28.2% cases, tuberculous endometritis in 2.6% cases and they observz. Cases of tuberculous endometritis were 11%. Another study showed results of secretory phase in 56.7% cases, proliferative phase in 16.6%, endometrial hyperplasias in 20% and non specific endometritis in 1.7% cases. Similarly, a study showed endometrial hyperplasias in 4.1% and non specific endometritis in 0.4% cases. Tuberculous endometritis as a cause of infertility is still a major problem in the developing countries, any woman having infertility and in which the cause cannot be ruled out, should be investigated for tuberculosis. In a study by Punyashetty et al, 3.9% cases were diagnosed as tuberculous endometritis but in contrary to this only 1(0.8%) case of tuberculous endometritis was diagnosed in our study.
It has been observed that endometrium may normally show leukocytic population comprising of i) intraepithelial lymphocytes ii) Interstitial stromal lymphocytes and macrophages iii) Lymphoid aggregates in stratum basalis. Morris et al suggested that the intraepithelial lymphocytes move towards the basalis and form lymphoid aggregates and then by menstruation are replenished.

According to a study by Geppert there was high lymphocytic concentration in cases of cyt glandular hyperplasias, pregnancy and endometrial carcinomas. There was low concentration in endometrial polypsis and adenomatous hyperplasias. In those females who had intake of oral contraceptives, lymphocytic count was high in endometrial biopsies.

In our study sporadic lymphocytic infiltrate was present in significant number of cases and intraluminal tufting was observed in majority of the cases suggesting the importance of these two parameters in infertility. The presence of lymphocytic infiltrate in infertility can have immunological basis for example as a result of antibody response or autoimmunity. Immunocytochemical studies can further explain the reasons for lymphocytic infiltrate in these patients.

Conclusion

Endometrial biopsy shows not only the hormone response of endometrium but also gives additional information about local factors of endometrium concerning non-specific and specific infections, tuberculous endometritis, hyperplasias and anovulatory cycles. All these morphological features form the etiological basis of many cases of infertility. In this study the two important findings were presence of lymphocytic infiltrate in the stroma and intraluminal tufting within the glands.

References

4. MedlinePlus Encyclopedia Infertility