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ORIGINAL ARTICLE

Histomorphological Patterns of Endometrium in Infertility

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Abstract

Background Endometrium is the most sensitive indicator of ovarian function and endometrial biopsy is one of the most important investigations in infertility. The current study was carried out to investigate the histomorphological patterns of endometrium in infertile women and to compare the results with other similar studies.

Materials and Methods A cross-sectional study on 2,080 infertile women was carried out to find the incidence of various histomorphological patterns in hematoxylin-eosin stained sections of endometrium and compare them with other Indian studies.

Results In the current study majority of cases (88.50 %) were of primary infertility; the highest number of cases was in the age group of 21–30 years and the oldest patient was of 50 years age. The various abnormalities observed were anovulatory endometrium (15.75 %), inadequate proliferative (1.90 %), inadequate secretory (9.52 %), glandulostromal disparity (GSD) (4.21 %), hyperplasia (1.10 %), and endometritis (1.63 %). In 3.0 % cases menstrual cycle history was not available and curettage was done at inappropriate period of the cycle in 11.63 %. Comparison with other studies revealed the results matching with some and differing with others.

Conclusion In the current study, anovulatory endometrium and luteal phase defect are the major causes of infertility, and tuberculous endometritis, non-specific endometritis and GSD are minor contributing factors. These are treatable causes. Premenstrual endometrial biopsy, if accompanied by information of menstrual cycle and date of biopsy, can be a

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very reliable diagnostic tool for hormonal dysfunction and intrinsic endometrial factors in infertility.

Keywords Infertility · Endometrium · Glandulo-stromal disparity · Luteal phase · Sterility · Histomorphological patterns

Key Message

Premenstrual endometrial biopsy if accompanied by information of menstrual cycle and date of biopsy can be useful diagnostic tool for hormonal dysfunction and intrinsic endometrial factors in infertility.

Introduction

Reproduction and perpetuation are features of living beings. Inability to do so is not only called Infertility but 'Infertility Crisis' because of the social, cultural, and psychological implications. Childlessness often creates enormous problems for the couples, especially for women who are generally blamed for infertility [1]. In 2010, the World Health Organization (WHO) defined it as, "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected intercourse" [2]. Primary infertility is failure to conceive at all, whereas secondary infertility is failure to conceive after having borne a child or abortion. It is a worldwide problem and approximately one marriage in ten is barren [3]. Infertility has been attributed to male factors 25 %, female factors 58 %, and unexplained in 17 % couples. Sometimes both male and female factors are present simultaneously [4]. However, in our country the infertility is a hidden social problem, where the females and not the males are solely held responsible. According to district level health survey (DLHS-3), Indian women who had infertility constitute 8.2 % of ever married women aged 15–49 years. Of these primary and secondary infertility were 6.3 and 1.9 %, respectively [5].

The purpose of investigating the infertile couple is to assess their chance of achieving pregnancy and to identify the factors amenable to treatment [6]. Female infertility may occur due to disturbances involving any part of genital system or parts of the central nervous system that control the ovaries hormonally [7]. Endometrium is the mirror of hypothalamus, pituitary, and ovarian function as well as bed and bread of the early developing embryo. It is the soil for the fertilized ovum to be implanted and is the end product of the hormonal complex and thus reflects the dysfunction of the complex in morphological abnormalities beside the local disease. To clarify the causes of infertility, an impressive array of diagnostic tests are available to clinicians [7]. Almost all functional disturbances involved in infertility result in morphological changes in the endometrium since hormone levels fluctuate depending upon various biorhythms, the histological examination of the endometrial biopsy is the most reliable parameter for evaluating the cause of infertility [8].

Materials and Methods

In the current study, 2,080 samples of endometrium over a period of thirteen years, received with the clinical diagnosis of infertility, primary or secondary, were included. The current study was a cross sectional study. All endometrial biopsies were processed by paraffin tissue processing, sections of 5 microns thickness were cut and stained with Hematoxylin and Eosin (H&E). The stained sections were studied under the microscope in view of the menstrual cycle, date of last menstrual period (LMP) and date of dilatation and curettage (D&C). For dating of the endometrium, the criteria described by Dallenbach Hellweg [9] were applied and endometrial specimens were divided into following groups:

1. Proliferative phase
   - Proliferative normal: early, mid, and late (biopsy done in proliferative phase of the cycle).
   - Inadequate proliferative (endometrial glands comparable to those in early or mid proliferative phase were found while the biopsy was done in secretory phase or late proliferative phase).
   - Proliferative-anovulatory (endometrial glands comparable to those in late proliferative phase while the biopsy was done in secretory phase).
   - Hyperplasia: simple and complex.
2. Secretory phase
   - Secretory normal (dates were matched with the menstrual cycle ±2 days).
   - Inadequate secretory/luteal phase defect (secretory changes lagging behind by two or more days of the menstrual cycle).
   - Secretory changes with glandulo-stromal disparity (GSD) (glandular and stromal changes were discordant).
3. Endometritis
   - Acute
   - Chronic nonspecific
   - Tubercular

All the cases included in the study group were divided into two major groups as primary infertility (Group 1) and secondary

infertility (Group 2). Statistics was applied to deduce significance wherever available with the help of SPSS biostatistics software version 19. The results of current study were compared with similar Indian studies.

Results

In a total of 2,080 endometrial biopsies studied, 1,841 (88.50 %) cases presented with primary infertility and the remaining 239 (11.50 %) cases with secondary infertility.

Age of Infertility

In primary infertility group, the youngest patient was 18 years old and eldest was 46 years, with an average age of 26.77. In secondary infertility cases, the youngest patient was 21 years old and eldest was 50 years, with an average age of 31.20 years. In primary infertility group maximum 762 cases (41.39 %) belonged to the age group of 21–25 years. In secondary infertility group maximum 81 cases (33.89 %) belonged to the age group of 26–30 years.When the number of cases in different age groups was compared in primary and secondary infertility, the difference was found to be highly significant statistically (P value < 0.001) as shown in Table 1.

Duration of Infertility

Duration of infertility analyzed in all 2,080 cases. Though the period of infertility ranged between 1 and 27 years, the maximum 817 cases were found to have a duration of 4–6 years. In the duration of 4–6 years there were 754 cases of primary infertility (mean $\pm$ SD $= 4.97 \pm 0.797$) and 63 cases of secondary infertility (mean $\pm$ SD $= 5.03 \pm 0.822$). When the mean age in different duration of primary and secondary infertility groups was compared, the difference was found to be highly significant statistically (P value < 0.001).

Endometrial Patterns

The study is based on one cycle one biopsy basis. The morphological patterns of endometrium have been divided into four subtypes- proliferative phase, secretory phase, endometritis, and hyperplasia. The 2,080 endometrial biopsies included, showed secretory pattern in 1,446 (69.52 %) cases followed by proliferative pattern in 574 (27.60 %) cases. Endometritis was seen in 41 (1.98 %) and hyperplasia in 19 (0.90 %) cases.

Morphological Patterns of Endometrium in Primary and Secondary Infertility

Secretory endometrium was seen in 1,283 (69.70 %) cases of primary infertility and 163 (68.20 %) cases of secondary infertility. Proliferative endometrium was seen in 501 (27.21 %) cases of primary infertility and 73 (30.54 %) cases of secondary infertility. Thus, the commonest endometrial phase was secretory phase in both study groups ($P = 0.252$) which was statistically not significant. Also there was no statistical difference in occurrence of different types of endometrium in primary and secondary infertility cases ($P > 0.05$).

The cases with proliferative endometrium in both the study groups were further sub-divided into four types as shown in Table 2.

1. Proliferative phase-normal (P): In primary infertility this subtype was seen in 199 (39.72 %) cases while in secondary infertility this subtype has maximum number of cases 43 (58.90 %). It is not advisable to do

Table 1 Age distribution among primary and secondary infertility patients ($n = 2,080$)

Age in years	Primary infertility			Secondary infertility		
	No. (%)	Mean age (years)	SD	No. (%)	Mean age (years)	SD
18–20	91 (4.94)	19.88	0.39	0	–	–
21–25	762 (41.39)	23.44	1.36	36 (15.06)	23.97	1.23
26–30	689 (37.43)	27.95	1.49	81 (33.89)	28.60	1.51
31–35	215 (11.68)	32.94	1.50	79 (33.05)	32.97	1.58
36–40	65 (3.53)	37.77	1.42	37 (15.48)	38.05	1.58
41–45	18 (0.98)	42.83	1.46	4 (1.68)	41.75	0.50
46–50	1 (0.05)	46.0	–	2 (0.84)	48.50	2.12
Total	1,841 (100)	26.77	4.57	239 (100)	31.20	5.01
P value for mean age (years)	–	<0.001	–	–	<0.001	–

For qualitative data i.e. no. of cases, P value $= < 0.001$

endometrial biopsy in proliferative phase in cases of infertility.

2. Inadequate proliferative phase (IP): In primary infertility this subtype was seen in 29 (5.79 %) cases and in secondary infertility, 4 (5.48 %) cases belonged to this subtype.
3. Proliferative phase-anovulatory (P-AN): In primary infertility this subtype has maximum number of 249 cases (49.70 %). In secondary infertility this subtype was seen in 24 (32.88 %) cases of all proliferative cases.
4. Proliferative phase-without history (LMP, MC): In primary infertility this subtype was seen in 24 (4.79 %) cases and 2 (2.74 %) cases of secondary infertility of all proliferative cases.

When the occurrence of different types of proliferative phase endometrium was compared in between primary and secondary infertility, the difference was found to be statistically significant ($P = 0.019$).

The cases with secretory phase endometrium in both the study groups were further sub-divided into four types as shown in Table 3.

1. Secretory phase-normal (S): In primary and secondary infertility this subtype has maximum number of cases, 1,049 (81.77 %) and 121 (74.24 %)respectively.
2. Inadequate Secretory phase (IS): In primary infertility this subtype was seen in 142 (11.07 %) cases and in secondary infertility 23 cases (14.11 %) of all secretory cases belonged to this subtype.
3. Secretory phase with GSD: In most of the cases, glands were showing the secretory changes corresponding with 18th to 20th day and stromal changes with 21st to 22nd day of a normal 28 days cycle. It was seen in 61 (4.75 %) cases of primary infertility and 12 (7.36 %) cases of secondary infertility of all secretory cases.
4. Secretory phase-without history (LMP, MC): In primary infertility this subtype was seen in 31 (2.41 %) cases and 7 (4.29 %) cases of secondary infertility of all secretory cases.

Table 2 The endometrial biopsy in proliferative phase ($n = 574$)

Histopathological pattern	Primary infertility No. (%)	Secondary infertility No. (%)
Proliferative phase-normal (P)	199 (39.72)	43 (58.90)
Inadequate proliferative phase (IP)	29 (5.79)	4 (5.48)
Proliferative phase-anovulatory (P-AN)	249 (49.70)	24 (32.88)
Proliferative phase-without history (LMP, MC)	24 (4.79)	2 (2.74)
Total	501 (100)	73 (100)
P value	0.019	

Table 3 The endometrial biopsy in secretory phase ($n = 1,446$)

Histopathological pattern	Primary infertility No. (%)	Secondary infertility No. (%)
Secretory phase-normal (S)	1,049 (81.77)	121 (74.24)
Inadequate secretory phase (IS)	142 (11.07)	23 (14.11)
Secretory phase, GSD	61 (4.75)	12 (7.36)
Secretory phase-without history (LMP, MC)	31 (2.41)	7 (4.29)
Total	1,283 (100)	163 (100)
P value	0.088	

Table 4 The endometrial biopsy in endometritis ($n = 41$)

Histopathological Pattern	Primary infertility No. (%)	Secondary infertility No. (%)
Acute endometritis (AE)	1 (2.63)	0
Chronic nonspecific endometritis (CE)	6 (15.79)	0
Tuberculous endometritis	31 (81.58)	3 (100)
Total	38 (100)	3 (100)
P value	1.000	

When the occurrence of different types of secretory phase endometrium was compared between primary and secondary infertility, the difference was not found to be significant statistically ($P = 0.088$).

Out of the total 2,080 cases, tuberculous endometritis was seen in 34 cases comprising 1.63 %. In primary infertility with endometritis, maximum number of cases 31 (81.58 %) had tuberculous endometritis and it was the only inflammatory cause in secondary infertility. ZN staining was negative. In primary infertility acute endometritis (AE) was seen in only 1 case (2.63 %) and chronic non-specific endometritis in 6 (15.79 %) cases while no case of acute or chronic endometritis was seen in secondary infertility as shown in Table 4.

Hyperplasia in infertility was seen in 19 cases out of the total 2,080 cases comprising 0.91 %. In primary infertility simple hyperplasia was seen in 17 (89.47 %) cases and complex hyperplasia in 2 cases (10.53 %).

Excluding the cases of proliferative and secretory phase without menstrual history and endometritis, anovulatory phase was seen in 325 (18.75 %) cases while ovulatory phase was seen in 1,408 (81.25 %) cases. Among the proliferative cases, proliferative-anovulatory has maximum number of 273 (84 %) cases. Among the ovulatory cases, adequate secretory phase was seen in maximum number of cases 1,170 (67.52 %), while deficient secretory phase was seen in 238 (13.73 %) cases as shown in Table 5.

Table 5 Endometrial morphological changes ($n = 1,733$)

Endometrial change	No. of cases	%
(1) Anovulatory	325	18.75
(a) Inadequate proliferative	33	
(b) Proliferative-anovulatory	273	
(c) Hyperplasia	19	
(2) Ovulatory	1,408	81.25
(a) Adequate secretory phase	1,170	
(b) Deficient secretory phase		
Inadequate secretory phase	165	
GSD	73	
Total	1,733	100

Discussion

Human endometrium is an important site for implantation of young fertilized ovum. Female infertility poses a complex problem to which a simple answer is rarely forthcoming. A battery of tests is essential to detect where the defect lies.

Endometrial biopsy in infertility studies is not only the simplest, quickest, cheapest and useful method of determining the occurrence of ovulation, but it also yields valuable supplementary information about the utero-ovarian endocrine relation of the particular woman. It is far more valuable than can be obtained by more difficult, inadequate, cost ineffective and complicated hormone assays.

The current study is based upon a comprehensive study of 2,080 endometrium from infertile women. The various observations have been discussed and compared with other Indian studies on the following pattern:

Incidence

Incidence of primary and secondary infertility endometrium among total 2,080 endometrium included in this study was 88.5 % and 11.5 %, respectively, which were nearly similar to the study of Abbasi et al. [10] which showed 89.4 % primary and 10.6 % secondary infertility cases. In the current study primary:secondary infertility ratio was 7.69:1; Abbasi et al. [10] observed ratio of 8.4:1 which is slightly higher as compared to our study.

Age

Most of the infertile patients presented within the most fertile age group. This observation is similar to that of other workers. Abbasi et al. [10] and Zawar et al. [11] also reported the largest number of cases in the age group of 21–30 years. Girish et al. [6] reported largest number of cases in the age group of 21–25 years. In the current study, mean age was 27.27 years, which is higher than other previous studies that can be explained on the basis of late marriages and change in the education status over the years.

Duration

In the current study, the highest number of 817 cases (39.28 %) was in the duration of 4–6 years. Zawar et al. [11] observed highest 42.6 % in 2–3 years of infertility in primary cases and 40 % in 6–7 years in secondary infertility.

Variation in duration is probably due to gradually increasing consciousness, changing working pattern, education and social status of the people in a developing country like India.

Endometrial Patterns in Infertility

The various endometrial histopathological patterns in the different Indian studies have been compared in the Table 6.

In the current study, proliferative phase was seen in 27.21 % of primary infertility cases and in 30.54 % of secondary infertility cases. In primary infertility, proliferative phase reported by Zawar et al. [11] was 29.7 % and Girish et al. [6] reported 27.8 %, which are nearly similar with our study. In secondary infertility, proliferative phase reported by Sanyal et al. [12] was 31 %, which is nearly similar with our study. The condition can be treated with ovulation inducing agents and appropriate estrogen therapy.

In the current study, secretory phase was seen in 69.70 % of primary infertility cases and in 68.20 % of secondary infertility cases. In primary infertility, secretory phase reported by Padubidri et al. [13] was 70.0 % which is nearly similar with our study (69.70 %). In secondary infertility, secretory phase reported by Zawar et al. [11] was 66.7 % and by Padubidri et al. [13] 65.9 %, which are slightly lower than in our study (68.20 %).

In the current study, secretory phase was reported in 69.52 % of total infertility cases, which is nearly similar with Gupta et al. [14] who reported secretory phase in 69.24 % of infertile women in their study.

In the current study anovulatory phase was seen in 18.75 %, while ovulatory phase in 81.25 % which is nearly similar with the study of Sareen et al. [15], Jadhav and Raichur [16] and Shetty [17]. But only Shastrabudhe et al. [7] subdivided anovulatory phase in three categories and deficient secretory phase into two categories which is similar to the current study pattern.

In the current study, adequate secretory phase was seen in 67.52 % which is nearly similar with the study of

Table 6 Comparison of percentage of different morphological patterns in Indian studies with the present study

Endometrial change	Shetty [17]	Gupta et al. [14]	Sareen [15]	Jadhav and Raichur [16]	Krishnamohan et al. [19]	Shastrabudhe et al. [7]	Zawar et al. [11]	Girish et al. [6]	Present study
Anovulatory									
(a) Inadequate proliferative	14.11	16.9	19	25	7.5	15.8	28.2	32.3	1.90
(b) Proliferative-anovulatory						14.0			15.75
(c) Hyperplasia	11.1	5.9	–	–	2.5	4.4	–	5.5	1.10
Ovulatory									
(a) Adequate secretory phase	74.8	60.4	40	75	80.0	46.5	47.4	56.7	67.52
(b) Deficient secretory phase	–	8.1	39	–	7.5	–	20	–	–
Inadequate secretory phase	–	–	–	–	–	8.8	–	–	9.52
GSD			–	–	–	7.0	–	–	4.21

Gupta et al. [14]; luteal phase defect in 13.73 % which is nearly similar with the study of Shastrabudhe et al. [7]. If adequate secretory phase is seen, it means that the endometrium is properly getting prepared for implantation but deficient secretory phase needs correction.

In the current study, tuberculous endometritis was seen in 1.68 % of primary infertility cases and 1.25 % of secondary infertility cases. In total cases of infertility, tuberculous endometritis was 1.63 %. The incidence of tuberculous endometritis in our study was lower as compared to other studies and nearly matching with the study of Sabharwal [18], who reported incidence of tuberculous endometritis as 1.34 %. It may be because of improved health care facilities over the years.

The differences in the histomorphological patterns of endometrium (Table 6) in various studies may be related to the differences in the geographical pattern and population and period of study.

Limitation of the study: Only endometrial patterns were studied. The other factors responsible for infertility (like endocrinopathies, tubal factors, endometriosis, etc.) were not studied.

Potential bias of the study: Menstrual history was not available in 64 cases (3 %) and endometrial biopsy was performed in proliferative phase of the cycle in 242 cases (11.63 %), which is not advisable in the infertility cases.

Conclusion

Histopathological study of endometrium can be an effective screening test in infertility if it is done in the premenstrual phase with proper information regarding the menstrual cycle, date of LMP and date of biopsy along with hormones or drugs given. Hormonal disturbances if present in the patients are reflected in the endometrium in the form of anovulatory cycle, inadequate proliferative/secretory phase, secretory GSD along with intrinsic abnormalities like endometritis. It is a useful investigation in infertility.

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Compliance with ethical requirements and Conflict of interest The present study is a retrospective as well as prospective cross-sectional study based on reported endometrial biopsies received from the clinicians as a part of routine investigation in infertile females. There are no ethical issues involved in this study. The authors have no conflict of interests.

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