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ENDOMETRIAL BIOPSIES;
INTER-OBSERVER VARIABILITY IN INTERPRETATION OF ENDOMETRIAL BIOPSIES IN INFERTILE WOMEN

Sabeen Nasir[1], Muhammad Mumtaz Khan[2], Naveed Sharif[3], Sadaf Alam[4], Sara Ziaullah[5], Sajjad Ahmad[6]

1. MBBS, M.Phil (Histopathology)
Assistant Professor
Department of Pathology
RIphah International University, Islamabad.
2. MBBS, M.Phil. (Histopathology)
Professor
Department of Pathology
RIphah International University, Islamabad.
3. MBBS, M.Phil (Histopathology)
Assistant Professor
Department of Pathology
Khyber Medical College, Peshawar.
4. MBBS, M.Phil (Histopathology)
Assistant Professor
Department of Pathology
RIphah International University, Islamabad.
5. MBBS, M.Phil (Histopathology)
Assistant Professor
Department of Pathology
RIphah International University, Islamabad.
6. MBBS, M.Phil. Ph.D (Histopathology)
Professor and HOD
Department of Pathology
RIphah International University, Islamabad.

Correspondence Address:
Dr. Muhammad Mumtaz Khan
Professor, Pathology Department
Peshawar Medical College
Warsak Road, Peshawar, Pakistan
mmumtazkhan@gmail.com

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ABSTRACT… Background: In histopathology, inter-observer variability is frequently encounter leading to diagnostic dilemma. Endometrial biopsies are one of them where multiple factors including hormonal influences make the interpretation difficult. The aim of the article was to find the interobserver variability level between two consultants on endometrial biopsies by applying kappa and ICC analysis. **Study Design:** Prospective study. **Setting:** Department of Pathology Peshawar Medical College Peshawar from Health Care Centre, University Town, Peshawar. **Period:** March to August 2013. **Methods:** This study consisted of 102 endometrial biopsies of infertile women on 22nd or 23rd day of menstrual cycle. All cases were examined by two consultants separately and formed their opinions independent of each other according to Noye's criteria. Their opinions were categorized as those in agreement, with minor disagreement and with major difference in opinion. **Results:** Agreement of opinion was established only in 34 (33.3%) cases. There was disagreement in 68 (66.7%) of cases. Out of these 68 cases, 46 (68%) belonged to the category of major conflicting opinion. In case of minor conflicting opinion, there was difference in specific day of the phase of menstrual cycle. The Kappa coefficient and ICC statistics was performed which gave the overall results as fair agreement. **Conclusion:** The main cause of disagreement was difficulty in applying the criteria for effects of hormonal influences on endometrial biopsies leading to subjective interpretation.

Key words: Inter-Observer Variability, Female Infertility, Endometrium.

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INTRODUCTION

The endometrium has a diverse morphological spectrum influenced by multiple factors including age,[1] endogenous and exogenous hormones,[2] urogenital hygiene and pregnancy.[3]

The histologic features of "normal" endometrium change with a woman's age in line with hormonal effects going through the premenarchal, reproductive, perimenopausal, and postmenopausal phases.[4,5] In biopsy specimens, the combination of these cyclical changes along with artifacts and limited sampling can make normal patterns difficult to interpret.[6]

Another factor adding to the variability in interpretation of endometrial biopsies in developing countries is that the exact age of the patient, her clinical and menstrual history, hormonal intake and relevant investigations are usually not available, so the pathologist has to base decisions on the scanty information. This adds to diagnostic variability and consultants may have different or sometimes conflicting opinions on the same slide creating loopholes for subjective interpretation. However, in fertility clinics the decision for endometrial biopsy is taken after thorough investigations of the patient so that they come with all the necessary details.[7]

The diagnostic variability can be both intra- and interobserver. Most of the work on variability in interpretation of endometrial biopsies has been done on malignant lesions.[2,8] However, one of the studies has found moderate disagreement in the histological dating of endometrium in fertile and

infertile women.[9]

The aim of the article was to assess the level of variability between two consultants in interpreting endometrial biopsies of infertile women.

MATERIAL AND METHODS

This prospective study consisted of endometrial biopsies of 102 infertile women (both primary and secondary) referred to Department of Pathology Peshawar Medical College Peshawar from Health Care Centre, University Town, Peshawar from March to August 2013. The present study was approved by the Institutional Ethical Committee of Peshawar Medical College.

The inclusion criteria were primary and secondary infertile women who went through diagnostic laparoscopy with their spouses having normal semen analysis reports. Socio-demographic data including age, type of infertility, complaints and years of infertility were recorded on a predesigned proforma after obtaining consent from the patient.

Endometrial biopsy was taken on 22nd or 23rd day of their menstrual cycle by Dilatation and Curettage (D&C) under aseptic conditions according to standard protocols. The specimen was fixed in 10% buffered formalin and sent to Peshawar Medical College Laboratory for further processing. Thin sections at 5-6 micron were cut and stained with Hematoxylin & Eosin for morphological studies.

All the 102 cases were examined by two consultants separately and formed their opinions independent of each other according to Noye's criteria.[10] Their opinions were categorized as those in agreement, with minor disagreement and with major difference in opinion. We statistically analyzed the data by Kappa and ICC analysis using SPSS version 20.

RESULTS

This study consisted of 102 cases of infertile women out of which primary were 58 (57 %) and secondary 44(43 %). The mean age of the patients was 28.6 (±5.15) and it ranged from 16 to 42years. Out of 102 cases, 58 (56.9%) were of primary infertility while 44 (43.1%) were of secondary infertility.

Regarding reporting of endometrial biopsies by consultants, agreement of opinion was established only in 34 (33.3%) cases. However, in majority of the cases, there was disagreement 68 (66.7%). Furthermore, out of these 68 cases, 46 (68%) cases belong to category of major conflicting opinion.

The cases with major conflicting diagnoses were related to various groups of endometrial pathology (Table-I).

In case of minor conflicting opinion, there was difference of opinion over the specific day of the phase of menstrual cycle. (Table-II)

The Kappa coefficient statistics was performed on all the cases to determine the value of agreement of opinion which came out as 0.383 (Table-III) and labeled as fair agreement. The ICC analysis showed 0.51 agreement (Table-IV).

DISCUSSION

The endometrial biopsy is very precious for an infertile woman and a lot depends on its correct diagnosis especially in cases of primary infertility.[11] The level of disagreement between consultants can be of value in identifying problems lying in the interpretation of biopsies. The main reason for variability in diagnosing endometrial biopsy is subjective interpretation of Noye's method which does not have precise enough objective criteria.[12]

Both the pathologists involved in this study routinely reported on endometrial biopsies. We found that overall interobserver reliability for pathologists assigning a date to a histological specimen was quite good when endometrial biopsies were at extreme of its phases, i.e., either in proliferative or late secretory phase. There was complete agreement among the two consultants in 33.3% of such cases.

Observer I Opinion	No.	Observer II Opinion	No.
Benign Secretory Endometrium	1	Basal Endometrium	2
Disordered Proliferative Endometrium	1		
Benign Secretory Endometrium	1	Complex Hyperplasia	4
Disordered Proliferative Endometrium With Superimposed Secretory Change	1		
Late Secretory Phase	2		
Late Secretory Phase	2	Early Secretory Phase	5
Disordered Proliferative Endometrium With Super imposed secretory changes	2		
Irregular Maturation of Endometrium	1		
Weak Proliferative (Inactive) Endometrium	1	Fragment of Endocervix	1
Weak Secretory Endometrium	1	Glandular Breakdown	1
Disordered Proliferative Endometrium	11	Discordance between gland and stroma signifying hormonal Imbalance	18
Chronic Granulomatous Inflammation	1		
Interval Phase Endometrium	1		
Early Secretory Phase	1		
Late Secretory Phase	2		
Simple Cystic Hyperplasia without Atypia	2		
Disordered Proliferative Endometrium	2	Interphase	3
Mid Secretory Phase	1		
Mixed Proliferative and Secretory Pattern Probably due to Hormonal Effects	1	Irregular Maturation	7
Mid Secretory Phase	2		
Late Secretory Phase	3		
Weak Secretory Endometrium with Pseudodecidualization	1		
Weak Secretory Endometrium with Pseudodecidualization	1	Mid Secretory	2
Late Secretory Phase	1		
Disordered Proliferative Endometrium	3	Proliferative Phase	3

Table-I. Distribution of major conflicting diagnosis

Observer I Opinion	No.	Observer II Opinion	No.
Early Secretory Phase 17/18	1	Early Secretory Phase 16/17	1
Early Secretory Phase 19/20	1	Early Secretory Phase 17/18	1
Mid Secretory Phase 21/22	3	Mid Secretory Phase 19/20	12
Late Secretory Phase 22/23	5		
Late Secretory Phase 23/24	3		
Late Secretory Phase 24/25	1		
Late Secretory Phase 22/23	3	Mid Secretory Phase 20/21	3
Late Secretory Phase 23/24	1	Mid Secretory Phase 21/22	4
Late Secretory Phase 24/25	3		
Early Secretory Phase 19/20	1	Late Secretory Phase 22/23	1

Table-II. Details of minor conflicting diagnosis

Kappa	Agreement
<0	Less than chance agreement
0.01-0.20	Slight agreement
0.21-0.40	Fair agreement
0.41-0.60	Moderate agreement
0.61-0.80	Substantial agreement
0.81-0.99	Almost perfect agreement

Table-III. Interpretation of Kappa

Symmetric Measures					
		Value	Asymptotic Standardized Error[a]	Approximate T[b]	Approximate Significance
Measure of Agreement	Kappa	.383	.054	10.436	.000
N of Valid Cases		102			

Intraclass correlation coefficient							
	Intra class Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.348[a]	.166	.507	2.070	101	101	.000
Average Measures	.516[c]	.285	.673	2.070	101	101	.000

Table-IV. Intra class correlation coefficient (ICC)
(Its value is between 0 and 1. The more it is closer to 1, the better is the inter observer reliability. Use the bold value)

In this study, minor conflicts in diagnosis with a difference of 1 to 2 days was 21.6% and major conflicts as out of phase diagnosis was found in 45.1% of cases. Other studies also reported 20%–40% biopsies as "in-phase" or "out-of-phase" when read by different pathologists.[9,13] In this study, we applied ICC and kappa coefficient as measures of variability because these methods measure chance-corrected proportional agreement. Although reliability in assignment of a date as measured by ICC was moderate, agreement about the diagnosis of "out of-phase" based on these readings as measured by the Kappa statistic was fair agreement. Disagreement of 1 or 2 days in assigning dates is not significant in fertile as compared to infertile women, because a disagreement of 1 or 2 days could easily result in "in-phase" or "out-of-phase" endometrium which is important for calculating luteal phase defect. This relatively small disagreement results in substantial diagnostic variability.[9]

In this study, we found that variability in endometrial morphological dating was greater during the mid-luteal phase, i.e., window of implantation, than the late luteal phase as reported by another study. These variation in the histological appearance of the endometrium during the window of implantation may point to hormonal influences a cause of infertility.[14] The results of this study and other studies give a clue that current histological methods for examining the endometrium in women presenting for infertility evaluation are not useful in clinical decision making because even with low interobserver variation, even the small changes in endometrial biopsy interpretation may lead to significant outcomes.[15,16] Therefore, further elaboration of criteria for diagnosing endometrial biopsies during the mid-luteal phase may provide insights into the interpretation of variability and may help reach pathologists at a consensus diagnosis.

CONCLUSIONS

Our consensus was identical in proliferative, early and late secretory phases because they have definitive identification criteria.

Regarding other entities disagreement was mainly due to lack of objective criteria leading to subjective interpretation which can be minimized through formation of detailed objective criteria.

REFERENCES

1. Alhassan A, Abaidoo CS: **Effect of maternal age on endometrial morphology among Ghanaian infertile women,** Journal of Medical and Biomedical Sciences 2012, 1:9-13.

2. Deligdisch L: **Hormonal pathology of the endometrium, Modern pathology:** An official journal of the United States and Canadian Academy of Pathology, Inc 2000, 13:285-294.

3. Noyes RW, Hertig AT, Rock J: **Dating the endometrial biopsy,** American journal of obstetrics and gynecology 1975, 122:262-263.

4. Trevoux R, Brux Jd, Bergeron C: **Biology of normal aging endometrium edited by Lorrain J,** Plouffe L, Ravnikar VA, Speroff L, Watts NB. New York, NY, Springer, 1994, p.

5. Dallenbach-Hellweg G: **Histopathology of the endometrium.** Edited by New York, Springer-Verlag,

1987,.

6. Mazur MT, Kurman RJ: Introduction. **In: Diagnosis of endometrial biopsies and curettings.** Edited by New York, NY, Springer New York, 1995, p. pp. 1-6.

7. **Diagnostic evaluation of the infertile female: a committee opinion,** Fertility and sterility 2015, 103:e44-50.

8. Gilks CB, Oliva E, Soslow RA: **Poor interobserver reproducibility in the diagnosis of high-grade endometrial carcinoma,** The American journal of surgical pathology 2013, 37:874-881.

9. Myers ER, Silva S, Barnhart K, Groben PA, Richardson MS, Robboy SJ, Leppert P, Coutifaris C: **Interobserver and intraobserver variability in the histological dating of the endometrium in fertile and infertile women, Fertility and sterility 2004,** 82:1278-1282.

10. Noyes RW: **The underdeveloped secretory endometrium,** American journal of obstetrics and gynecology 1959, 77:929-945.

11. Nandedkar SS, Patidar E, Gada DB, Malukani K, Munjal K, Varma A: **Histomorphological patterns of endometrium in Infertility,** Journal of Obstetrics and Gynaecology of India 2015, 65:328-334.

12. Li TC, Dockery P, Rogers AW, Cooke ID: **How precise is histologic dating of endometrium using the standard dating criteria?,** Fertility and sterility 1989, 51:759-763.

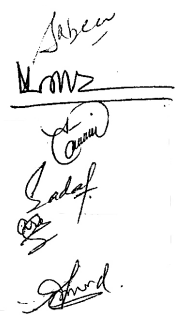
13. Castelbaum AJ, Wheeler J, Coutifaris CB, Mastroianni L, Jr., Lessey BA: **Timing of the endometrial biopsy may be critical for the accurate diagnosis of luteal phase deficiency,** Fertility and sterility 1994, 61:443-447.

14. Coutifaris C, Myers ER, Guzick DS, Diamond MP, Carson SA, Legro RS, McGovern PG, Schlaff WD, Carr BR, Steinkampf MP, Silva S, Vogel DL, Leppert PC: **Histological dating of timed endometrial biopsy tissue is not related to fertility status,** Fertility and sterility 2004, 82:1264-1272.

15. Smith S, Hosid S, Scott L: Endometrial biopsy dating. **Interobserver variation and its impact on clinical practice,** The Journal of reproductive medicine 1995, 40:1-3.

16. Mahajan N: **Endometrial receptivity array: Clinical application,** Journal of human reproductive sciences 2015, 8:121-129.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Sabeen Nasir	Designing, analysis and drafting.	
2	M. Mumtaz Khan	Analysis, revising and final approval.	
3	Naveed Sharif	Interpretation.	
4	Sadaf Alam	Analysis and revising	
5	Sara Ziaullah	Revising	
6	Sajjad Ahmad	Drafting and revising.	