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A Study On Endometrial Histomorphological Patterns And Glycogen Correlation In Female Infertility

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Abstract

Introduction: Infertility is disease of reproductive system characterised by failure to achieve pregnancy after 12 months or more of unprotected regular intercourse.

Aim and objectives: To study various histo-morphological patterns in endometrium in different types of infertility and to assess endometrial glycogen content in cases presenting with infertility.

Material and Methods: This cross sectional study was carried for period of 1 year on 150 endometrial biopsies of patients with infertility. Biopsies were subjected to tissue processing techniques followed by Hematoxylin & Eosin and Periodic Acid Schiff stains .

Result: Out of 150 cases, there were 59.3% cases of primary infertility and 40.7% of secondary infertility. Microscopic examination revealed Anovulatory cycles (34.66%), Ovulatory cycles (36.66%),Luteal phase defect (19.3%), Gland stroma asynchrony (4.66%), Disordered proliferative phase (3.3%) and Chronic non-specific endometritis (1.33%). Glycogen scoring showed 23.33% of cases with ovulatory cycles associated with inadequate endometrial preparation and 13.33 % cases showed adequate glycogen content.

Conclusion: Histopathological study of endometrium can be an effective screening test in infertility. Hormonal disturbances if present are reflected in the endometrium as depletion of glycogen which can be corrected by hormonal therapy, which increases the fertility potential.

Keywords: Endometrial biopsy, Female Infertility, Histomorphology, Glycogen Content

Introduction

Infertility is defined as a disease of the reproductive system characterized by failure to achieve pregnancy after 12 months or more of unprotected regular intercourse[1]. Primary infertility is not being able to conceive at all, whereas secondary infertility is defined as failure of conception after having borne a child or abortion [2]. Infertility is attributed to female factors in 58%, male factors in 25% and is unexplained in 17% of cases[2]. Investigating the infertile couple is necessary to determine their chance of achieving pregnancy and to identify the factors responsible for it[3]. A wide array of diagnostic tests including the hormonal assays are available at the disposal of clinicians. Hormonal tests are not widely available and are an economic burden on the patient[4]. Dating of the endometrium done by its histological examination is used clinically to assess hormonal status or documentation of ovulation [5]. Glycogen in endometrial gland is a direct source of nutrition for the early conceptus and depletion of it may result in inadequate endometrial preparation around the time of implantation, and hence causes infertility[6]. Glycogen shows cyclical changes under influence of hormones like oestrogen and progesterone (mainly). Therefore, endometrial glycogen analysis can help detect glycopenia which indicates immaturity and inadequate

preparation of endometrium which prevents implantation of fertilised ovum and subsequent growth of an embryo, thus contributing to infertility. The present study was done to assess the various endometrial histomorphological patterns and glycogen content of endometrium in cases presenting with infertility.

Materials and Methods: This prospective study (Descriptive cross sectional study) was carried out over a period of one year [from July 2023 to June 2024] on 150 endometrial Biopsies of patients presenting with infertility received in the Histopathology section , Department of pathology at J.L.N. Medical College, Ajmer, Rajasthan.

Inclusion criteria: Endometrial biopsies from patients presenting with primary or secondary infertility was included.

Exclusion criteria: Inadequate biopsies and Cases previously worked up for infertility and on treatment. Endometrial biopsies received in 10% neutral buffered formalin, were fixed followed by tissue processing. The sections were routinely stained with Harris Hematoxylin and Eosin stain and special stain like PAS.

Microscopic Examination: For dating of the endometrium, the criteria described by Dallenbach Hellweg7 was applied and endometrial specimens were divided into following categories according to their microscopic histological findings:

ANOVULATORY CYCLES	OVULATORY CYCLES	ENDOMETRITIS
Proliferative Phase	Secretory Phase	Acute
Hyperplasia	Luteal Phase Defect	Chronic nonspecific
	Glandulo-stromal disparity	Tubercular

Glycogen content was graded according to Arzac and Blanchet17 method as :

O	Negative reaction (no staining)
+	Very small granules
++	Coarse granules
+++	Small masses
++++	Large masses

Intensity of glycogen grading was done as : Mild (0 and 1+) , Moderate(2+) , High(3+ and 4+)

Results

Out of 150 cases**,** Primary infertility was more prevalent, affecting 59.3% of the participants (89 cases), while secondary infertility accounted for 40.7% of the cases(61 cases).

Age of Infertility The study revealed that the majority of participants (36.0%) belonged to the 26–30 years age group, followed by 21–25 years (30.6%) and 31–35 years (20.7%). The least represented age group was 41+ years, accounting for only 2.0% of the total cases.

In the present study, primary infertility was most prevalent in the youngest age group (21–25years),accounting for 73.9% of cases, while secondary infertility increased with age, reaching 100.0% in the 41+ years group. The 26–30 years age group had the highest total number of cases (36.0%), with primary infertility still dominating (66.7%). However, in the 31–35 and 36–40 years groups, secondary infertility became more frequent (61.3% and 56.3%, respectively). The association between age groups and infertility type was statistically significant (p= 0.002).

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Table1: Age group wise distribution of cases between the two groups

	TYPE OF INFERTILITY					
Age groups	Primary		Secondary		Total	
	Count	Percent(%)	Count	Percent(%)	Count	Percent(%)
21 - 25	34	73.9	12	26.1	46	30.7
26 - 30	36	66.7	18	33.3	54	36
31 - 35	12	38.7	19	61.3	31	20.7
36 - 40	7	43.8	9	56.3	16	10.7
41	0	0	3	100	3	2
Total	89	59.3	61	40.7	150	100

Duration of infertility

The duration of infertility was most commonly 1–5 years (60.0%), followed by 6–10 years (25.3%). Longer durations of infertility (26+ years) were less frequent, representing only 2.0% of the cases.

Menstrual Patterns in Infertility

Normal menstrual cycles were the most common pattern (68.0% of total cases). Oligomenorrhea was observed in 25.3% of participants.Menorrhagia was less frequent(1.3% of cases) .Polymenorrhea cases (5.3% of total) showed a slight predominance of primary infertility (62.5%).

Table 2: Menstrual cycle characteristics in the study group.

	TYPE OF INFERTILITY					
Menstrual Cycle	Primary		Secondary		Total	
	Count	%	Count	%	Count	%
Menorrhagia	1	50	1	50	2	1.3
Normal	64	62.7	38	37.3	102	68
Oligomenorrhea	19	50	19	50	38	25.3
Polymenorrhea	5	62.5	3	37.5	8	5.3
Total	89	59.3	61	40.7	150	100

Microscopic Findings In Infertility:

Anovulatory cycles (34.66%) and ovulatory cycles (36.66%) were the most frequent microscopic findings. Luteal phase defect was observed in 19.3% of cases.

Table 3: Microscopic findings between primary and secondary infertility groups

MICROSCOPIC FINDING	Primary		Secondary		Total	
	Count	%	Count	%	Count	%
Anovulatory	34	65.4	18	34.6	52	34.66
Chronic non-specific endometritis	2	100	0	0	2	1.3
Disordered Proliferative Phase	2	40	3	60	5	3.3
Gland stroma asynchrony	5	71.4	2	28.6	7	4.66
Luteal phase defect	14	48.3	15	51.7	29	19.3
Ovulatory	32	58.2	23	41.8	55	36.66
Total	89	59.3	61	40.7	150	100

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Glycogen scoring In Endometrial Biopsies

Anovulatory cycles predominantly showed low-moderate glycogen levels (1+ and 2+ scores comprising 73.1% of anovulatory cases) whereas Ovulatory cycles demonstrated better glycogen accumulation, with 63.6% showing scores ≥2+. Luteal phase defects (19.3% of total) exhibited the widest distribution, including the highest proportion of 4+ scores (13.8% of LPD cases)The distribution patterns of endometrial glycogen stores in various setting showed statistically significant difference (p-value = 0.01).

Table 4: Distribution of Glycogen Scoring (PAS Stain) by Microscopic Findings

MICROSCOPIC FINDINGS	GLYCOGEN SCORING (PAS STAIN)					
	0	1+	2+	3+	4+	Total
Anovulatory	12	22	16	2	0	52
Chronic non-specific endometritis	0	1	1	0	0	2
Disordered Proliferative Phase	1	0	2	1	1	5
Gland stroma asynchrony	3	1	3	0	0	7
Luteal phase defect	4	6	9	6	4	29
Ovulatory	4	13	18	17	3	55
Total	24	43	49	26	8	150

P value=0.01

Correlating microscopic findings with Glycogen Scoring

Glycogen scoring showed 23.33% of cases with ovulatory cycles associated with inadequate endometrial preparation. However, 13.33 % of cases showed ovulatory cycles with adequate glycogen content, hence other unknown factors like tubal factors, cervical factors, male factors etc can be responsible for infertility. Therefore, on the basis of microscopic features and glycogen scoring the possible etiological breakdown of the 150 study cases of infertility is as follows-Hormonal disturbances (50.66%), Anovulatory causes (34.66%), Infectious causes (1.33%) and other possible factors (tubal factors, cervical factors, maleinfertility etc.) in 13.33%.

Figure 1 Anovulatory Endometrium showing Grade 0 glycogen . PAS (10x)

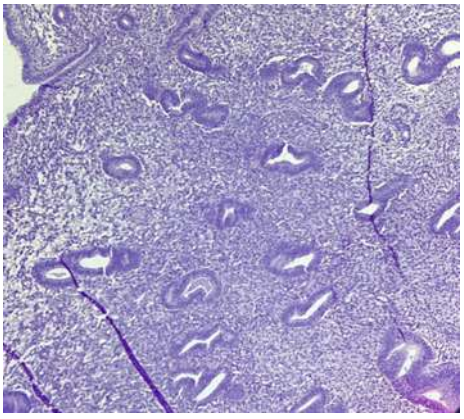

Figure 2 Anovulatory Endometrium showing Grade 1+ glycogen . PAS (40x)

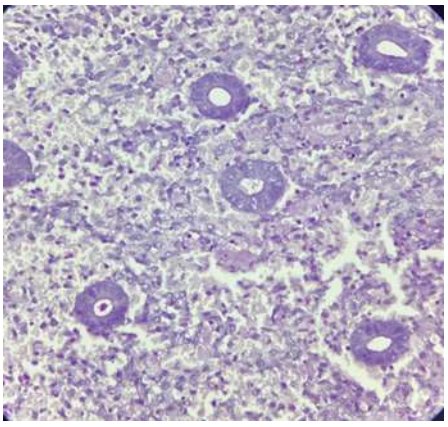

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Figure 3. Secretory Endometrium showing Grade 0 glycogen (glycopenia). PAS (40x)

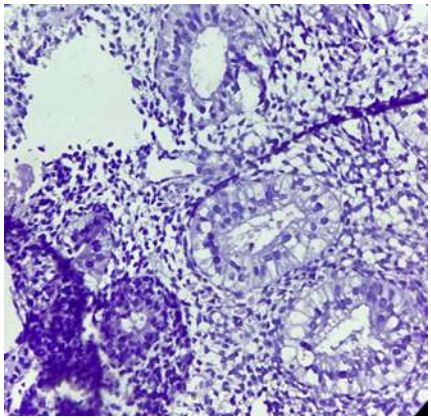

Figure 4. Secretory Endometrium showing Grade 1+ glycogen (Fine granules). PAS (40x

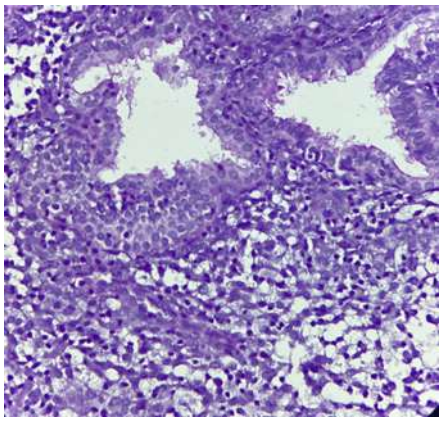

Figure 5. Secretory Endometrium showing Grade 2+ glycogen (coarse granules), PAS (40x)

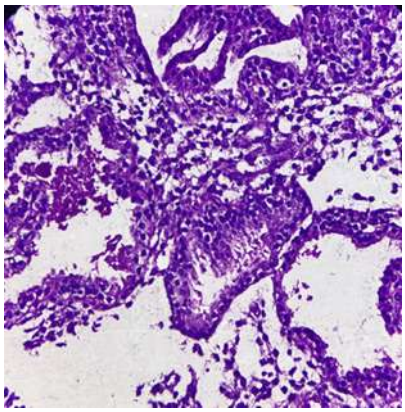

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Figure 6. Secretory Endometrium showing Grade 3+ glycogen (Small masses). PAS (40x)

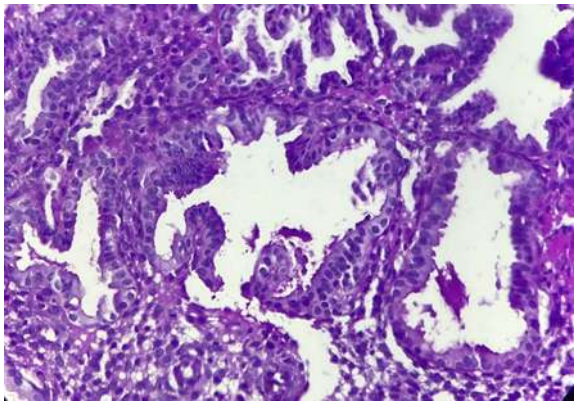
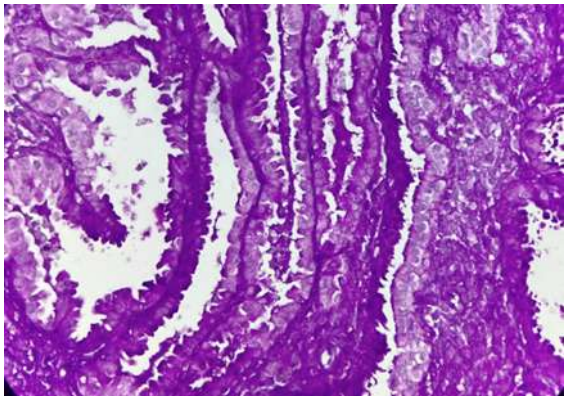


Figure 7. Secretory Endometrium showing Grade 4+ glycogen (Large masses).PAS (40 x)



Discussion

In the present study, the study population had a mean age of 28.97 years, with primary infertility being more prevalent (59.3%) than secondary infertility (40.7%). This aligns with studies by Nandedkar SS et. al. (2015)9 who reported average age of 26.77 years in their study and with Ahmed et al. (2018)10 (29.91) years) but is lower than that reported by Anita P. Javalgi et al. (2022)11 (35.6 years) possibly due to differences in study population demographics or regional fertility trends. In the present study, the mean duration of infertility was 6.76 years in primary infertility and 5.89 years in secondary infertility with no statistically significant difference (p = 0.361). The most frequent duration was 1-5 years (60%), followed by 6--10 years (25.3%), while prolonged infertility (>10 years) was rare. In the present study we observed 30.99% of endometrium in ovulatory phase having glycogen content below 2+ or showing glycopenia.

Nandedkar et al. (2015)9 established the relevance of endometrial glycopenia, reporting similar phase dependent patterns. However, their cohort showed even more pronounced deficiency in proliferative phase (89% low glycogen) compared to our study. This consistency across studies validates glycopenia as a persistent histopathological marker in infertility evaluations.

Conclusion

Endometrial biopsy along with glycogen estimation is a safe and cost effective tool to guide the clinicians regarding the suspected cause of infertility and choose an appropriate future course of action thus, helping childless couples without the additional economic burden of expensive hormonal tests. Anovulatory infertility as depicted by premenstrual proliferative endometrium (34.66% of cases in present study) may require treatment with ovulation inducing drugs.

Microscopic examination combined with endometrial glycogen estimation revealed possibility of hormonal disturbances in 50.66% of cases (including ovulatory cycles with glycopenia,

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luteal phase defects, gland stroma asynchrony and disordered proliferative phase) indicating necessity of progesterone based hormonal therapy. Infectious aetiology accounting for 1.33% cases in the present study need appropriate regime to increase chances of conception.

Patients with ovulatory cycles and adequate glycogen content (13.33% cases) should be investigated for other possible factors like tubal causes and male causes of infertility.

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