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Original Research Article

A Study on Female Infertility: Various Endometrial Histomorphological Patterns and Correlation with Glycogen Content of Endometrial Glands

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Abstract

Background: Infertility is a significant global health issue affecting approximately 8–10% of couples. A successful pregnancy requires physiological equilibrium and a receptive endometrium. Glycogen in the endometrial glands provides essential nutrition for the early conceptus; its depletion (glycopenia) may lead to implantation failure.

Objective: To study various endometrial histomorphological patterns in primary and secondary infertility and assess endometrial glycogen content to determine its role in infertility.

Methods: This study analyzed 150 cases of infertility. Endometrial biopsies were subjected to histopathological examination and Periodic Acid-Schiff (PAS) staining to grade glycogen content (Grade 0 to 4+) using the Arzac and Blanchet method.

Results: Primary infertility accounted for 59.3% of cases. The most common histomorphological patterns were ovulatory (36.7%) and anovulatory (34.7%) endometrium. Glycogen analysis revealed that 34% of ovulatory endometrium exhibited glycopenia. There was a statistically significant association between microscopic endometrial patterns and glycogen scoring (p=0.01), though no significant difference in glycogen content was found between primary and secondary infertility groups.

Conclusion: Endometrial biopsy combined with glycogen estimation is a valuable diagnostic tool. Glycopenia is a demonstrable cause of infertility even in ovulatory cycles, highlighting the necessity of evaluating glycogen stores in infertile women.

Keywords: Infertility, Endometrium, Gycopenic Endometrium.

Introduction

Infertility is defined by the World Health Organization (WHO) as a disease of the reproductive system characterized by the failure to achieve pregnancy after 12 months or more of unprotected regular intercourse.[1] It affects approximately 48 million couples worldwide, with one in ten marriages being barren. [2,3] In India, infertility affects 8.2% of married women aged 15–49 years.[5]

A successful pregnancy relies on a finely orchestrated physiological equilibrium. The endometrium serves as the end organ for ovarian hormones and the site of implantation. Investigating the endometrium via biopsy provides evidence of ovulation, luteal phase adequacy, and intrinsic pathology such as tuberculous endometritis. [5] A critical factor in endometrial receptivity is glycogen content. Glycogen in endometrial glands is a direct source of nutrition for the early conceptus. [6] Under the influence of progesterone, endometrial cells increase glycogen stores during the secretory phase to support implantation. When the endometrium fails to produce adequate glycogen, a condition known as "Glycopenic Uteri," it may result in implantation failure and subsequent infertility. [6]

This study aims to assess various endometrial histomorphological patterns and correlate them with the glycogen content of the endometrium in cases of primary and secondary infertility.

Materials and Methods

Study Design and Population: The present study included 150 cases of women presenting with infertility. The patients were categorized into primary infertility (women who have never conceived) and secondary infertility (failure to conceive after a previous pregnancy).

Study Place and Duration: The study was conducted at SNMC, Jodhpur for the period of 1 year from Dec 2023 to Nov 2024

Endometrial Biopsy and Histology: Endometrial tissue was obtained via curettage/biopsy. Tissue samples were processed for routine histological examination to determine the phase of the menstrual cycle (proliferative or secretory) and identify pathologies.

Dating of the endometrium was performed based on histological criteria to assess hormonal status.

Glycogen Estimation (PAS Staining): Glycogen content was estimated using the Arzac and Blanchet method [7] utilizing Periodic Acid-Schiff (PAS) staining. This histochemical technique oxidizes glycols to aldehydes, which react with Schiff reagent to produce a magenta color indicating glycogen presence.

Grading of Glycogen: [7]

Glycogen deposits were graded based on intensity and distribution:

- **Grade 0:** Negative reaction (No detectable glycogen).
- **Grade 1 (+):** Very small granules (Minimal glycogen).
- **Grade 2 (++):** Coarse granules (Moderate glycogen).
- **Grade 3 (+++):** Small masses (Good amount of glycogen).
- **Grade 4 (++++)** Large masses (Intense deposits).

Statistical Analysis: Data were analyzed to compare age, clinical presentation, and histopathological findings between primary and secondary infertility groups. Statistical significance was determined using Chi-square tests and t-tests, with p-values calculated to assess associations.

Results

Demographic and Clinical Profile: The mean age of the study population was 29.21±5.3 years. Primary infertility was more prevalent (56.7%, n=85) than secondary infertility (43.3%, n=65). A statistically significant age difference was observed, with the mean age for primary infertility being 27.21±4.10 years compared to 31.83±5.71 years for secondary infertility (p=0.001). The mean duration of infertility was 6.32 years for primary and 5.17 years for secondary cases however the difference was not statistically significant (p = 0.88).

The most common clinical presentation was irregular menstruation in 51.3% of participants. Other common clinical presentation included hypothyroidism (14.67%) and oligomenorrhea (20.67%).

Histomorphological Findings: On Microscopic examination revealed the following endometrial patterns: [Table no. 1]

- Ovulatory (Secretory): 36.7%
- Anovulatory (Proliferative/Anovulatory): 34.7%
- Luteal Phase Defect (LPD): 19.3%
- Other findings: Disordered proliferative phase (3.3%), gland-stroma asynchrony (4.7%), and chronic non-specific endometritis (1.3%).

There was no statistically significant difference in the distribution of microscopic findings between primary and secondary infertility groups (p=0.236).

Glycogen Content Analysis Glycogen scoring using PAS staining showed distinct patterns based on histomorphology (p=0.010): [Table no. 2]

- **Anovulatory Cycles:** Predominantly showed low glycogen levels, with 73.1% of cases scoring 1+ or 2+.
- **Ovulatory Cycles:** Demonstrated better accumulation, with 63.6% showing scores ≥2+. However, 34% of ovulatory cases still exhibited glycopenia (scores <2+).
- **Luteal Phase Defect:** Exhibited a wide distribution, but 35% of LPD cases showed glycopenia.

When comparing infertility types, glycogen scores did not differ significantly between primary and secondary infertility (p=0.497). [Table no. 3]

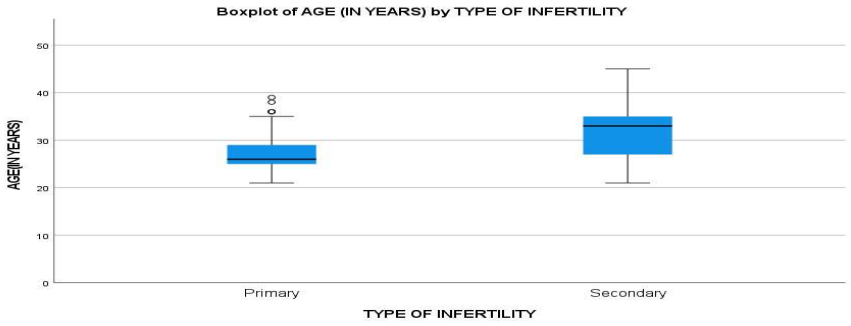

Figure 1: Boxplot showing age statistics of both primary and secondary infertility in the present study.

Table 1: Microscopic findings between primary and secondary infertility groups.

	Type of Infertility					
	Primary		Secondary		Total	
	Count	Percent	Count	Percent	Count	Percent
Anovulatory	33	63.5%	19	36.5%	52	34.7%
Chronic nonspecific endometritis	2	100.0%	0	0.0%	2	1.3%
Disordered Proliferative Phase	1	20.0%	4	80.0%	5	3.3%
Gland stroma asynchrony	5	71.4%	2	28.6%	7	4.7%
Luteal phase defect	14	48.3%	15	51.7%	29	19.3%
Ovulatory	30	54.5%	25	45.5%	55	36.7%
Total	85	56.7%	65	43.3%	150	100.0%
Sig.	0.236					

Table 2: Distribution of Glycogen Scoring (PAS Stain) by Microscopic Findings

Microscopic Finding	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
Sig.	0.010					

Table 3: Comparison of Glycogen Scoring between primary and secondary infertility

	Type of Infertility		
Glycogen Scoring (Pas Stain)	Primary	Secondary	Total
0	10	14	24
1+	29	14	43
2+	30	19	49
3+	12	14	26
4+	4	4	8
Total	85	65	150

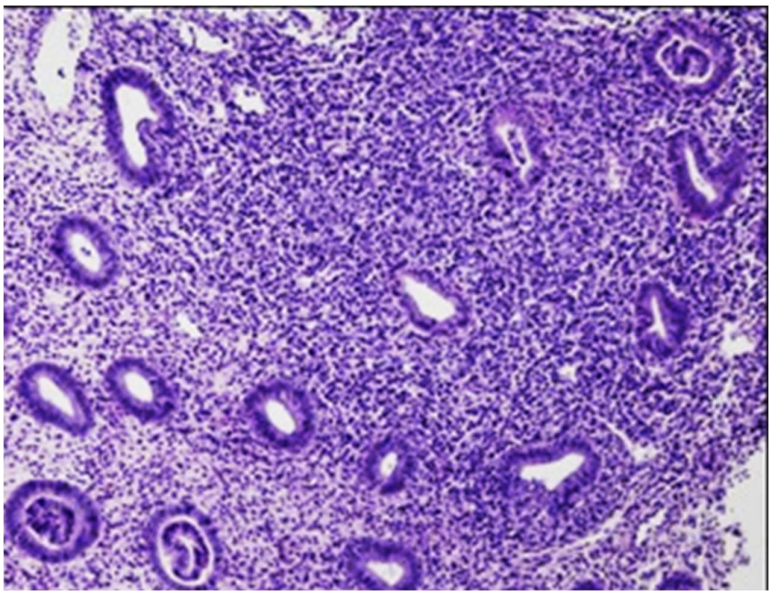

Figure 2: Chronic nonspecific endometritis (H&E 10x)

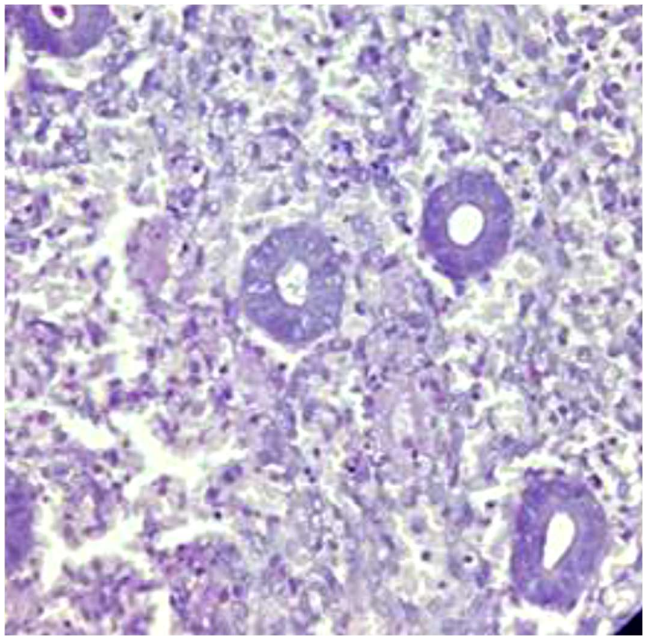

Figure 3: Anovulatory Endometrium with Grade 1+ glycogen store (PAS 40x)

Discussion

Demographics and Infertility Types: The study population's mean age (27.21 years) aligns with previous studies by Ahmed et al. [8] and Nandedkar et al. [9] The significant age gap between primary and secondary infertility suggests secondary infertility is often associated with advancing age and prior reproductive history.

The higher prevalence of primary infertility (56.7%) in this cohort is consistent with literature, though the proportion of secondary infertility (43.3%) was higher than in some comparable studies, potentially reflecting regional trends in pelvic inflammatory disease or delayed childbearing. [10,11]

Histomorphology and Glycogen Correlation This study highlights the critical link between endometrial histology and metabolic function. Glycogen accumulation typically progresses during the menstrual cycle, peaking in the secretory phase to support implantation. Our results confirmed this metabolic gradient, as ovulatory endometrium showed significantly higher glycogen stores than anovulatory samples.

However, a crucial finding is the presence of glycopenia in 34% of histologically "ovulatory" endometria. This aligns with Nandedkar et al. [9], who reported similar deficiencies, suggesting that histological evidence of ovulation does not guarantee functional adequacy for implantation. Additionally, 35% of cases diagnosed with Luteal Phase Defect showed glycopenia, reinforcing that low glycogen stores contribute significantly to implantation failure in LPD.

Clinical Implications: The presence of hyperglycogenemia in specific cases, such as those with Polycystic Ovarian Syndrome (PCOS), suggests that metabolic dysregulation (e.g., hyperinsulinemia) may also impair fertility, distinct from simple deficiency. The lack of significant difference in glycogen scoring between primary and secondary infertility indicates that endometrial glycogen deficiency is a common pathophysiological factor across infertility subtypes rather than a distinguishing feature.

Conclusion

Infertility remains a complex, multifactorial condition. This study demonstrates that histopathological evaluation of the endometrium, supplemented by histochemical estimation of glycogen, provides essential insights into reproductive failure.

Key Takeaways:

- Anovulatory cycles and Luteal Phase Defects are significant contributors to infertility.
- A substantial proportion of women with ovulatory cycles exhibit endometrial glycopenia, which may lead to implantation failure despite normal ovulation.

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