



Original Article

A study on glycogen content of endometrial glands in infertile women

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ABSTRACT

Keywords:

Endometrium;
Glycogen;
Infertility;

Background: Infertility is a public health problem worldwide. One of the important factors involved in infertility is the poor quality of endometrium which leads to death of the ovum before and after implantation. Glycogen is known to be a direct source of nutrients for the early conceptus and its depletion may result in inadequate preparation of endometrium around the time of implantation and leading to infertility.

Materials and methods: This is a prospective study conducted at a tertiary care hospital for 2 years. The study included 75 cases of infertility (primary and secondary). Relevant data were collected from all the 75 biopsied infertile cases during the study period. Periodic acid Schiff stain was performed on all cases to detect the amount of glycogen in the endometrium. The findings were compiled, analyzed, and compared with other studies.

Results: Primary infertility accounted for 77.3% and Secondary infertility 22.7% of the 75 cases. On histology, anovulatory cycles accounted for 52% of cases. In the remaining cases, 38.7% showed secretory phase, 4% cases each showed luteal phase defect and hyperplasia, and 1.3% tubercular endometritis. Glycogen content of the endometrium was (1+) in 54.6%, (2+) in 9.3%, (3+) in 9.3% and (4+) in 26.8% in the infertility patients. Glycopenia was seen in 12% of the 75 cases studied.

Conclusions: Endometrial factors are important causes of infertility and depletion of glycogen, that can be corrected by hormonal therapy to improve the fertility potential needs to be evaluated in all cases of infertility.

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INTRODUCTION

Infertility affects approximately 8%–10% of couples worldwide and India alone accounts for around 25% of cases.¹ Infertility is a complex problem requiring a battery of tests to detect the defect. Endometrial biopsy not only is a simple, economical, and valuable method of determining ovulation but also provides information about any defect in the hypothalamic-ovarian endocrine chain.² One of the important factors involved in infertility is the poor quality of endometrium which leads to the death of the ovum before

Table 1: Age wise distribution of the cases

Age group	Number of cases	Percentage(%)
21 – 25	26	34.6 %
26 – 30	32	42.6 %
31 – 35	15	20.0 %
36 – 40	2	2.8%
Total	75	100%

and after implantation. Glycogen is known to be a direct source of nutrient for the early conceptus and its depletion may result in inadequate preparation of endometrium around the time of implantation, and hence causes infertility.³ Scarcity in the literature on the role of glycogen content in the endometrium as an etiological factor from rural south India prompted us to undertake this study to explore the role of glycogen content in the endometrium along with other factors like duration of infertility, the pattern of menstruation and other clinical features in causing infertility.⁴

MATERIALS AND METHODS

The present prospective study was conducted in a tertiary care hospital which caters to a rural population in and around Hoskote, for a period of 2 years from July 2018- July 2020. Ethical clearance was obtained from the institutional ethics committee for the study. The study included 75 cases biopsied to evaluate infertility (primary and secondary). Patients who failed to conceive after one year of unprotected coitus following marriage were investigated as cases of primary infertility and patients who failed to conceive

after having prior conception were investigated as cases of secondary infertility. Detailed information of the clinical history of the menstrual cycle, last menstrual period, and obstetric history were obtained.

Inclusion criteria:

Endometrial biopsies from patients with primary or secondary infertility were included.

Exclusion criteria:

- Inadequate biopsies
- Cases previously worked up for infertility and on treatment.

Premenstrual endometrial tissues obtained from the obstetric and gynecology department were processed and subjected to routine processing. Haematoxylin and Eosin (H and E) and Periodic Acid-Schiff (PAS) stains were performed on all the cases and analyzed. Glycogen content was graded according to Arzac and Blanchet method as given below.⁵

0 = Negative reaction (no staining); + = Very small granules; ++ = Coarse granules; +++ = Small masses; ++++ = Large masses

0 and 1+ were taken as mild, ++ as moderate, +++ and ++++ were considered as high. The findings were compiled and analyzed in relation to the endometrial histology.

Table 2: Menstrual cycle: Distribution of normal and abnormal cycles

Menstrual cycle	Primary Infertility		Secondary Infertility	
	No. of cases	%	No. of cases	%
Normal	35	60.4%	12	70.6%
Abnormal				
Irregular	13	22.4%	02	11.8%
Oligomenorrhoea	01	1.7%	01	5.8%
Dysmenorrhoea	04	6.9%	0	0
Menorrhagia	05	8.6%	02	11.8%
Total	58	100%	17	100%

Table 3: Endometrial patterns in infertile cases

Menstrual cycle	Primary Infertility		Secondary Infertility		Total
	No. of cases	%	No. of cases	%	
Proliferative (Anovulatory)	32	55.2%	7	41.2%	39 (52 %)
Secretory Phase	22	37.9%	7	41.2%	29(38.7%)
Luteal phase defect	2	3.5%	1	5.8%	03(4%)
Endometritis (Tubercular)	1	1.7%	0	-	01(1.3%)
Hyperplasia (Disordered Proliferation & Simple Hyperplasia)	1	1.7%	2	11.8%	03(4%)
Total	58	100%	17	100%	75(100%)

Table 4: Glycogen grading in the Infertile cases – PAS stain

Glycogen content & Grade		Proliferative	Secretory	Luteal Phase defect	TB Endometritis	Hyperplasia	Total
0 (fig.1)	Mild	25	-	-	-	-	25(33.3%)
+ (fig. 2)		14	-	1	-	1	16(21.3%)
++ (fig. 3)	Moderate	-	03	2	-	2	07(9.3%)
+++ (fig. 4)	High	-	06	-	1	-	07(9.3%)
++++ (fig. 5)		-	20	-	-	-	20(26.8%)
Total		39	29	3	1	3	75(100%)

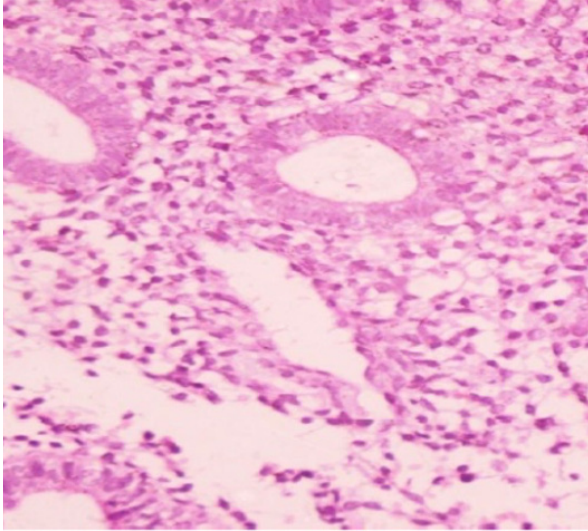


Figure 1: Grade 0: Proliferative phase showing negative reaction for PAS stain(40x)

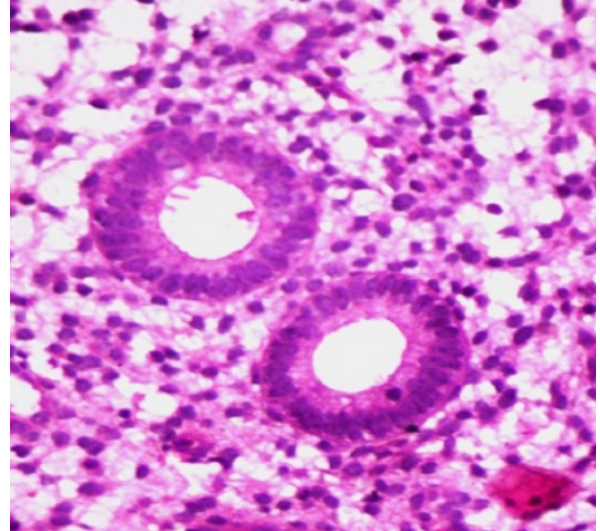


Figure 2: Grade +: Proliferative phase showing fine granules on PAS (40x)

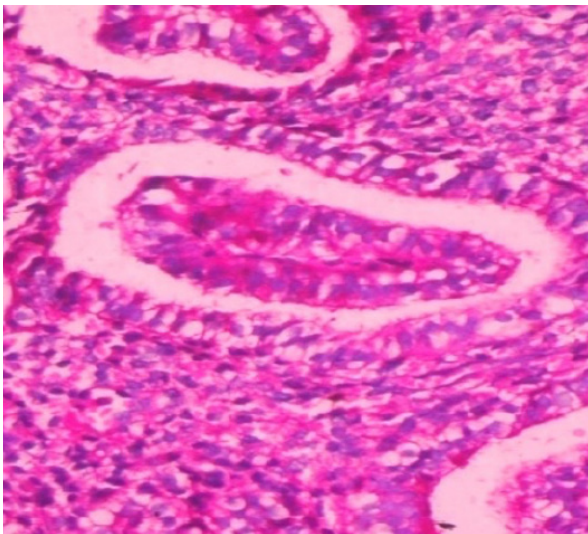


Figure 3: Grade ++: Secretory phase showing coarse granules on PAS stain (40x)

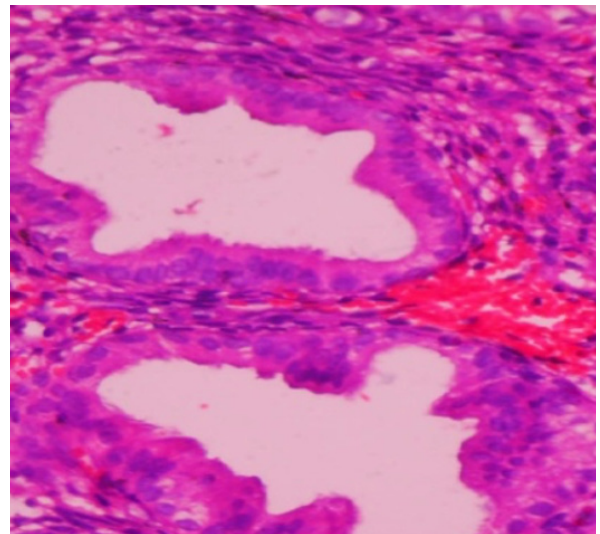


Figure 4: Grade +++: Secretory phase showing small masses on PAS stain(40x)

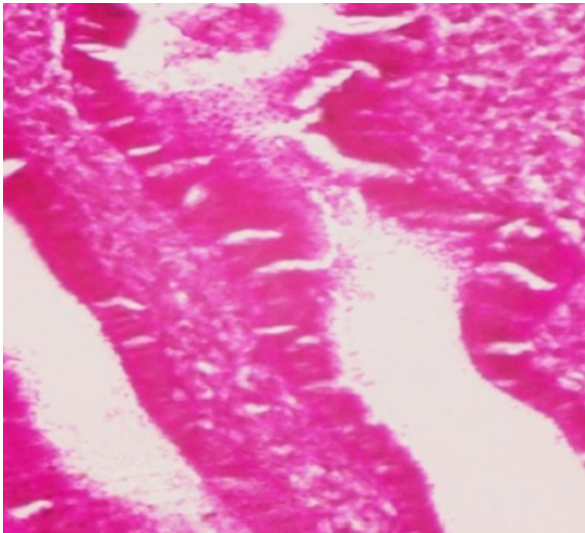


Figure 5: Grade ++++: Secretory phase showing large masses on PAS stain (100x)

All the data were collected in a proforma and entered into MS Excel sheets. Descriptive statistics like mean and percentage were used for the study. The findings obtained were analyzed and compared with similar studies in the literature.

RESULTS

Amongst 75 cases of infertility, 77.3% (n=58) of cases were of primary infertility and 22.7% (n=17) of cases were of secondary infertility. The majority of patients were in the age group of 26-30 years (Table.1). The youngest patient was 21 years old and the oldest was 37 years.

Among 58 cases of primary infertility, 35 cases (60.4%) had normal cycles and among 17 cases of secondary infertility, 12 cases (70.6%) had normal cycles. In the cases with primary infertility, irregular cycles, menorrhagia, dysmenorrhoea, and oligomenorrhoea were the abnormalities encountered. In Secondary infertility too, irregular cycles, menorrhagia, and oligomenorrhoea were noted as depicted in Table 2.

On histology, the most common finding was that of a proliferative pattern depicting anovulatory cycles. This was seen in 52% (n=39) of cases and was the most common pattern in both the primary and secondary infertility groups. A secretory pattern was observed in 38.7% of the 75 cases studied (n=29). This accounted for the next common finding in both primary and secondary infertility groups.

Luteal phase defect was seen in 4% of 75 cases studied. This accounted for 3.5% of primary and 5.8% of the secondary infertile groups. The hyperplasia group which included cases of both disordered proliferation and simple hyperplasia accounted for 4% of cases. This feature accounted for 1.7% of primary and 11.8% of secondary infertility cases. A single case of tubercular endometritis was encountered among the

primary infertility cases. The findings are highlighted in Table 3

PAS staining and interpretation were done with appropriate controls for checking the adequacy of staining where in endometrium showed mild glycogen in 54.6%, moderate in 9.3%, heavy in 9.3%, and intense in 26.8% of infertility patients.

DISCUSSION

In a rural hospital setup, where immunological and hormonal assay procedures are not easily available or affordable, endometrial biopsy is an important investigation for infertility.⁶ In our study, primary infertility was more common than secondary infertility i.e. 58 cases out of 75 cases (77.3%) studied. Similar findings have been documented by Kauret al⁷ (77.14%) and Chelab et al⁸ (71.90 %).

The mean age of infertile women in our study was 29 yrs. This is comparable to studies by Kafeelet al⁹ (29 years, range of 21-37 years) and Ahmed M et al¹⁰ (33 years, range 23-43). Cases beyond this age become less in view of the loss of hope by the couples, 2nd marriage, or taking up adoption.

In spite of biopsies sampled in the premenstrual phase, proliferative /anovulatory pattern was the most common cause of infertility. Similar findings were also observed by Girishet al⁴ from Shimoga and Ikeme et al¹¹ in Nigeria and Cheleb et al⁸ in Algeria. Other studies have found a secretory pattern to be more common which is an expected finding in a premenstrual biopsy. Polycystic Ovarian Disease (PCOD) which accounted for 12% of 75 cases explains the higher number of proliferative cases in our study.

Endometrial hyperplasia may be due to long-standing follicular persistence and a high level of unopposed estrogen. In the present study, endometrial hyperplasia accounted for 4% of the 75 cases. This is similar to the observations of Murmu et al⁶ (2.74%), Sabharwal et al¹² (2.66%), Shastrabudhe et al¹³ (4.4%), and Sharma et al¹⁴ (6.0%). Ahmed et al¹⁰ from Bangladesh who found a slightly higher incidence of 10.7%, analyzed data from various countries and found this feature to be lower in India compared to Pakistan and Nigeria where incidence was as high as 14% and 20% respectively.

Luteal phase defect may be the cause of infertility in ovulatory cycles. The diagnosis of luteal phase defect is based on Jones criteria correlating between the last menstrual period and endometrial dating. In the present study, a luteal phase defect was noted in 3 of the 75 cases (4%) studied. This is similar to that noted by Murmu et al⁶ who reported luteal phase defect in 8.2 % of the 79 cases studied. This is the present study accounted for 1 of the 58 (3.5 %) cases with primary infertility and 2 of the 17 (5.8%) cases with secondary infertility. In comparison, Murmu et

al6 noted a higher proportion of secondary infertility cases with luteal phase defects (16.7%). This could be due to the small sample size of secondary cases studied by them.

Tuberculous endometritis is still a major cause of infertility in developing countries and any woman with unexplained infertility should be investigated for tuberculosis. It accounted for 1.72% of our cases. Similar findings have been observed by Kafaelet al9 (0.8%) and Ahmed M etal¹⁰ (0.51%). In contrast, Punyashetty et al¹⁵ encountered a higher incidence of 3.9%. Variations in socioeconomic status and education could be factors responsible for the variations.

In the present study, PAS stain was done on all 75 cases. Glycogen deficiency (mild) on PAS stain is indicated by Grade 0 and +, moderate amount of glycogen as ++ and high glycogen is indicated by +++ and ++++. In our study glycogen depletion was seen in 41 cases (54.6%) whereas it was 43.3% in a study done by Girish et al⁴ and 50% in a study done by Sharma et al.¹⁴ A moderate amount of glycogen was observed in 9.3% in our study whereas it was 26.7% in a study done by Girish et al⁴ and 16.7% in a study done by Sharma et al.¹⁴ High glycogen content was observed in 36% of cases in our study whereas it was 30% in a study done by Girish et al⁴ and 33.3% in a study done by Sharma et al.¹⁴

Genital tract glycogen is unique in that unlike muscular glycogen, it is unaffected by either carbohydrate intake or exercise. Maeyama et al¹⁶ assessed the urinary pregnanediol and found a high correlation between the function of corpus luteum and endometrial glycogen deposition. Hughes in 1967 reported that glycogen is present in the highest concentration around the 17 to 20 the day of the cycle.¹⁷ Interpretation of the relative finding mentioned above should be hence be done in the context of the phase of the cycle as done below, where the glycogen content is known to be low in proliferative and high in secretory phases.

All 39 cases that showed a proliferative phase on histology all had a glycogen content of (0) and (+) grade. Similar findings have been documented by Sharma et al¹⁴ and Girish et al.⁴ In the 29 cases showing secretory phase on histology a majority (89.7%) of cases showed a grade (+++) or (++++) glycogen content. A similar finding of 92.3% was noticed by Sharma et al.¹⁴ Comparable results between the 3 studies can also be seen for luteal phase defect where all studies found reduced glycogen content of grade (+) or (++) and a slight predominance of grade (++) levels.

Unlike our study, the other studies did not report the glycogen grade for cases of tubercular endometritis or hyperplasia. In the present study, the single case of tubercular endometritis showed a secretory pattern on histology and correspondingly a glycogen grade of (+++). Endometrial hyperplasia, which is due to excess levels of estrogen can also modify the endometrial glycogen content.

In the present study, all the three cases studied had a lower glycogen content of (+) or (++).

Pradhan et al³ and Gupta et al¹⁸ have analyzed glycogen content in endometrial biopsies of infertile women in secretory phase and luteal phase defect where authors have reported a glycogen deficiency of 28.88% and 24.7% respectively. Similar findings have been noted in our study (18.7%). However, the documentation of glycopenia in 12% of all 75 cases (3 cases of secretory, 3 cases of hyperplasia, and 3 cases of luteal phase defect) studied presents the true population who would receive hormonal therapy and thereby have an improved fertility potential. In the remaining cases which showed a proliferative pattern, an additional endometrial biopsy may be required on a follow-up to identify the true nature of the deficiency.

CONCLUSION

Our study highlights the importance of estimating glycogen deficiency in the endometrium in cases with infertility in a rural hospital setup. Depletion of glycogen has been documented by studies in the past including the present study. As this factor can be corrected by hormonal therapy and thereby improve the fertility potential; it may be worthwhile to assess this parameter routinely in all cases of unexplained infertility. It needs to be ascertained in the future whether glycopenia is a primary feature in the biopsy or secondary to the various histological changes noted in the endometrium.

Conflict of interest: None

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