International Journal of Research in Medical Sciences
Shivappa P et al. Int J Res Med Sci. 2022 Aug;10(8):1663-1667
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20221976

Original Research Article

Glycopenic endometrium in infertility

Prateek Shivappa[1]*, Roma Isaacs[1], Kavita Mandrelle[2], Sunita Goyal[2]

[1]Department of Pathology, [2]Department of Obstetrics and Gynaecology, Christian Medical College and Hospital, Ludhiana, Punjab, India

Received: 06 February 2022
Accepted: 01 July 2022

***Correspondence:**
Dr. Prateek Shivappa,
E-mail: prateek1084@gmail.com

ABSTRACT

Background: Infertility is a global health problem affecting 8-10% couples worldwide. Endometrium is considered to be sensitive indicator of ovarian, pituitary and hypothalamic function. The endometrium, which fails to produce adequate amount of glycogen is termed as 'glycopenic uteri'. Glycopenic endometrium is said to be unfavourable for early blastocyst implantation leading to infertility in spite of ovulation. Endometrial aspiration/biopsy can be histologically dated based on the Dallenbach-Hellweg criteria which forms an essential part of histopathological examination of endometrium for infertility work-up. The aim of the study was to study the correlation of glycogen content with endometrial histomorphology in infertility.
Methods: Cross-sectional observational study in which one hundred twenty-two endometrial specimens sent as curetting/ biopsy were studied. The Glycogen content of endometrium was graded from + to ++++ as given by Arzac and Blanchet. Statistical analysis was done on SPSS version 26.0. The categorical variables were represented by count (percentage) and the continuous variables were represented by mean±SD. The Chi-square test was used to find the association of glycogen content with infertility, the various phases of the endometrium and age.
Results: Glycopenic endometrium was seen in 36.9% cases of infertility. Out of which, glycopenic endometrium was much more prevalent in patients with secondary infertility (47%) as compared to patients with primary infertility (35.1%).
Conclusions: Glycogen depletion in secretory phase results in inadequate preparation of endometrium at the time of implantation. Assessment of glycogen is considered to be an essential part of histopathological examination.

Keywords: Endometrium, Glycogen, Histopathological examination, Infertility

INTRODUCTION

Infertility is a global public health problem due to its complexity and difficulty in diagnosing, treating and preventing it. Infertility affects 8-10% couples worldwide.[1] One of the pathological factors of infertility is poor quality endometrium that leads to death of the ovum before and after implantation.[2]

Glycogen is believed to be the direct source of nutrients for the early conceptus from the time it enters the uterine cavity to the time it is actively supported by maternal blood stream. Endometrium undergoes cyclical change under the influence of estrogen and progesterone. In healthy persons, glycogen concentration was reported to be five- to ten times higher in the secretory phase than in the proliferative phase. The endometrium when fails to produce adequate amount of glycogen is termed as 'Glycopenic uteri'.[3] Glycogen makes its appearance in the glandular epithelium shortly before ovulation and increases progressively in quantity during the secretory phase of the endometrium. It shifts into the lumina of the glands along with the secretion. It is also present in the secretion escaping from the surface of the endometrium immediately before the menstruation. There is a slight reduction in the amount of glycogen in the epithelia of

the glands at this time. The glucose circulating in the blood is converted into glycogen and stored in the glands as glycogen which represents the most convenient and readily utilizable form of storage. At the time of implantation this is reconverted into a simple monosaccharide like glucose that could serve as an excellent nutritional basis for the blastocyst, before its actual implantation in the endometrium.[4] Since there was a scarcity in the literature on the role of glycogen content in the endometrium as a determinant of infertility in females, so the present study was undertaken to evaluate the role of glycogen content in endometrium.

METHODS

Cross-sectional observational study conducted in department Of pathology, Christian Medical College, Ludhiana, Punjab. One hundred twenty-two endometrial specimens sent as curetting/ biopsy were studied. The study period was 2 year 6 months. Retrospective period was from 1st October 2017 to 30th September 2018 and prospective period was from 1st October 2018 to 31st March 2020.

Inclusion criteria

Endometrial specimens sent for both primary and secondary infertility.

Exclusion criteria

Endometrial specimens for other causes and inadequate endometrial tissue.

Review of patient data

Relevant information of all the enrolled cases such as patient's age at marriage, menstrual history, last menstrual period, obstetric history and other clinical details were obtained from the histopathology request forms and hospital records.

The endometrial tissue was fixed in 10% formalin for 24 hours and routinely processed. 5-6 µ sections were cut and stained with hematoxylin and eosin (H and E), periodic acid schiff (PAS) and Periodic acid schiff with diastase (DPAS) for histochemical study of endometrium.[5,6]

The Glycogen content of endometrium is graded by Arzac and Blanchet criteria: 0 Negative reaction, +Very small granules, ++Coarse granules, +++Small masses and ++++Large amounts.[7]

Statistical analysis

It was done on SPSS version 26.0. The categorical variables were represented by count (percentage) and the continuous variables were represented by mean±SD. The Chi-square test was used to find the association of glycogen content with infertility, the various phases of the endometrium and age. Fisher-exact test was used for counts less than 5. The p value less than 0.05 was considered significant.

RESULTS

One hundred twenty-two endometrial specimens sent as curetting/ biopsy were studied. Primary infertility was found in 86% (105/122) women while secondary infertility was present in 14% (17/122) women. Majority of patients with primary infertility (79, 75.2%) as well as secondary infertility (12, 70.5%) were in the age group of 21-30 years. The mean duration of infertility was 5.6 years in overall cases. However, the mean age of women with secondary infertility were slightly older (29.2 years) and had longer mean duration of infertility of 6.7 years as compared to women with primary infertility whose mean age were 26.4 years and mean duration of infertility was 5.2 years.

Histopathological examination of endometrium

Endometrial dating was done by the criteria given by Dallenbach-Hellweg (1981) which involves number and type of endometrial glands, pseudostratification of nuclei, basal vacuolations, stromal edema, blood vessels, predecidualization and leukocytic infiltration.8 The histopathological patterns of endometrium showed predominance of secretory (S) phase (59%), followed by luteal phase defect (LPD) (25.4%), proliferative (P) phase (anovulatory phase, 9.8%), tuberculous (TB) endometritis (3.2%) and menstrual (M) phase (2.4%).

Glycogen content of endometrium

Glycogen content of endometrium was investigated by means of histochemical reactions because assessment of glycogen content forms an essential part of histopathological examination of endometrium. Glycogen content was graded according to Arzac and Blanchet criteria (1948).[7] Special stains such as PAS and DPAS were done to assess the glycogen content of endometrium in both glands and stroma. Glycopenic endometrium was depicted as negative reaction (grade 0 glycogen, Figure 1) and very small granules (grade 1+) while adequate glycogen was represented as coarse granules (grade 2+ glycogen), small masses (grade 3+ glycogen) and large amounts (grade 4+ glycogen, figure 2). Negative reaction (Grade 0 glycogen) was seen in 25 cases (20.5%), very small granules (grade 1+) in 20 cases (16.4%), coarse granules (grade 2+) in 28 cases (23%), small masses (grade 3+) in 27 cases (22.1%) and large amounts of glycogen (grade 4+) in 22 cases (18%). In this study, glycopenia was seen in 45/122, 36.9% cases of infertility (Table 1). Glycopenic endometrium was much higher in patients with secondary infertility (8/17, 47%) as compared to patients with primary infertility (37/105, 35.1%) (Table 1). However, this difference was not found to be statistically significant (p=0.384).

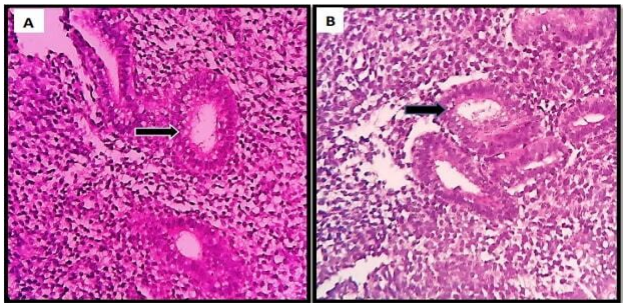

Figure 1: Photomicrograph showing endometrial glands with no glycogen granules (black arrow), (400X) grade 0- nil (glycopenic endometrium) (A) PAS; and (B) DPAS.

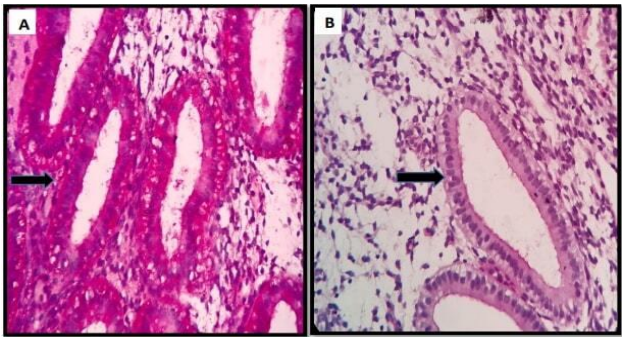

Figure 2: Photomicrograph showing glands with large amounts of glycogen particles (black arrow), (400X) grade 4- large amounts (A) PAS; and (B) DPAS.

Table 1: Distribution of glycogen content.

Glycogen content	Overall cases		Primary infertility		Secondary infertility	
	(n)	(%)	(n)	(%)	(n)	(%)
Negative reaction (grade 0)	25	20.5	20	19	5	29.4
Very small granules (grade 1+)	20	16.4	17	16.1	3	17.6
Coarse granules (grade 2+)	28	23	27	25.7	1	5.8
Small masses (grade 3+)	27	22.1	23	21.9	4	23.5
Large amounts (grade 4+)	22	18	18	17.1	4	23.5
Total	122	100	105	100	17	100

Table 2: Correlation of glycogen content in corresponding endometrial phases.

Glycogen content	Late proliferative		Luteal phase defect		Secretory phase						Menstrual phase	
					Early		Mid		Late			
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Negative reaction (grade 0)	5	41.7	8	25.8	1	5.3	5	10.4	1	20.0	2	66.7
Very small granules (grade 1+)	4	33.3	5	16.1	3	15.8	6	12.5	1	20.0	1	33.3
Coarse granules (grade 2+)	2	16.7	5	16.1	7	36.8	13	27.1	1	20.0	-	-
Small masses (grade 3+)	1	8.3	9	29.0	4	21.1	12	25.0	-	-	-	-
Large amounts (grade 4+)	-	-	4	12.9	4	21.1	12	25.0	2	40.0	-	-
Total	12		31		19		48		5		3	
P value	0.009		0.306		0.106		0.749		0.159		0.572	

Correlation of glycogen content in corresponding endometrial phases

Proliferative (anovulatory) phase showed glycopenic endometrium in (9/12, 75%) cases while adequate glycogen was seen in (3/12, 25%) cases of infertility. It was considered as one of the important causes of infertility and was statistically significant in its association with low glycogen content (p=0.009) (Table 2). Anovulation not only resulted in irregular proliferation of glands due to decreased estrogen levels but was also associated with glycogen deficiency which lead to delayed maturation of glands. Glycopenic endometrium was seen in (17/72, 23.6%) cases of secretory phase endometrium corresponding to dates in overall cases of infertility. Glycopenic endometrium was seen predominantly in late secretory phase (2/5, 40%) followed by mid secretory phase (11/48, 23%) and early secretory phase (4/19, 21%). The glycopenic endometrium was found to be much higher in luteal phase defect (13/31, 41.9%) as compared to secretory phase endometrium corresponding to dates (17/72, 23.6%) because of a poorly developed endometrium in luteal phase defect, though the association between both of them was not statistically significant (p=0.269) (Table

2). Glycogen depletion during secretory phase results in inadequate preparation of endometrium for implantation of fertilized ovum and hence is considered as one of the important causes of infertility.

DISCUSSION

The endometrium is a tissue of interest since it is the most favoured site for the implantation of the ovum. Endometrial glycogen is one of the most important factors for development of blastocyst in the early stages of gestation which is reconverted into a simple monosaccharide like glucose at the time of implantation.[9] Assessment of glycogen content in endometrium by histopathological examination is an important part of infertility work up as glycogen is present in the glandular secretions and is considered to be a direct source of nutrition for early conceptus.

Age distribution

Most common age group of infertility was from 21 years to 30 years which correlated with the studies done by Zawar et al, Ikeme et al, Girish et al, Kafeel et al, Nandedkar et al, Kaur et al and Sharma et al.[10-16]

Incidence of primary and secondary infertility

Majority (86%) of cases in this study had primary infertility and 14% had secondary infertility. This was similar to studies done by Zawar et al, Nandedkar et al, Kaur et al, Sharma et al and Murmu et al.[10,14,15-17] A study done in Nigeria by Ikeme et al showed a higher incidence of secondary infertility as compared to primary infertility.[11] Histopathological patterns of endometrium were recognized as per dating criteria by Dallenbach-Hellweg (1981) depending on the number and type of endometrial glands, glandular epithelial lining, blood vessels and stromal features. The histomorphological patterns of endometrium were divided into following subtypes- proliferative (anovulatory phase), secretory phase, luteal phase defect, tuberculous endometritis and menstrual phase. In this study, secretory phase endometrium (ovulatory endometrium) corresponding with dates was seen in (72/122, 59%) cases of infertility. Majority (48/122, 39.3%) of cases in secretory phase showed mid secretory phase endometrium followed by early secretory phase endometrium (19/122, 15.5%) and late secretory phase endometrium (5/122, 4.1%). Similar findings in which secretory phase endometrium was predominant pattern were observed by Zawar et al (2003), Ikeme ACC et al (2004), Kafeel S et al (2012), Nandedkar SS et al (2015), Sharma V et al (2016) and Murmu S et al (2017).[10,11,13,14,16,17]

Secretory phase endometrium means that the women is ovulating and there are good chances of conception in subsequent cycles. However, inspite of ovulatory endometrium defect may be present somewhere else, it can be due to luteal phase defect and depletion of glycogen that results in inadequate preparation of endometrium at the time of implantation and henceforth leading to infertility.

In this study, glycogen concentration was increased during secretory phase. Similar findings were observed by Zawar et al, Girish et al, Gupta et al, Nandedkar et al, Sharma et al, and Pradhan et al.[10,12,14,16,18,19]

There was a shift from predominantly anaerobic glycolysis during proliferative phase to predominantly aerobic glycolysis during progestational phase. Overall glycopenic endometrium constituted (45/122, 36.9%) cases of infertility which caused habitual abortion and therefore was much higher in patients with secondary infertility (8/17, 47%) as compared to patients with primary infertility (37/105, 35.1%). Glycogen deficiency during secretory phase was found in (17/72, 23.6%) cases of infertility. Zawar et al, Girish et al, Gupta et al, Nandedkar et al, Sharma et al, Pradhan et al and Achalkar showed glycopenic endometrium ranging from 20-30% while Gupta et al found glycopenic endometrium in higher number (45%) of cases.[10,12,14,16,18-21]

Glycogen deficiency was seen in (13/31, 41.9%) cases of luteal phase defect in overall cases of infertility which was similar to the studies done by Zawar et al, Girish et al and Sharma et al.[10,12,16] Hence, luteal phase defect alone was not responsible for infertility as glycopenia was found in as high as 41.9% of these patients, thereby emphasizing an important role of endometrial glycogen content to facilitate a successful gestational event.

Glycopenic endometrium was found in (9/12, 75%) cases of overall infertility and was found to be statistically significant (p=0.009). Gupta also found glycopenic endometrium in 65% cases in anovulatory endomentrium.[20]

CONCLUSION

The assessment of glycogen content of endometrium by histopathological examination is an essential part of infertility work up as glycopenia indicates immaturity and inadequate preparation of endometrium which prevents implantation of fertilized ovum and subsequent growth of an embryo, thus contributing to infertility. It can be corrected by hormonal therapy and improve fertility potential.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of Christian Medical College, Ludhiana, Punjab

REFERENCES

1. Purkayastha N, Sharma H. Prevalence and potential determinants of primary infertility in India:

Evidence from Indian demographic health survey. Clin Epidemiology Glob Health. 2021;9:162-70.
2. Padubidri VG, Daftary SN. Infertility and Sterility. Shaws Textbook of Gynaecology. 16th ed. New Delhi: Reed Elsevier India Private Limited; 2014: 237-262.
3. Rohatgi K, Singh VK, Rajvanshi VS. Study of endometrial glycogen in cases of dysfunctional uterine haemorrhage and subfertility. J Obstet Gynaecol India. 1977;27(6):905-10.
4. Girish CJ, Manjunath ML. Morphological patterns of endometrium in infertile woman a prospective study. Int J Appl Biol Pharm Technol. 2011;2:512-20.
5. Bancroft JD, Layton C. The hematoxylins and eosin. In: Suvarna KS, Layton C, Bancroft JD, eds. Bancroft's theory and practice of histological techniques. 8th edition. China: Elsevier; 2019: 126-137.
6. Layton C, Bancroft JD. Carbohydrates. In: Suvarna KS, Layton C. Bancroft JD, eds. Bancroft's theory and practice of histological techniques. 8th ed. China: Elsevier; 2019: 177-196.
7. Arzac JP, Blanchet E. Alkaline phosphatase and glycogen in human endometrium. J Clin Endocrinol Metab. 1948;8(4):315-24.
8. Dallenbach-Hellweg G. The Histopathology of the endometrium. Histopathology of the endometrium. 3rd ed. Hiedelberg: Spinger Verlag; 1981: 89-256.
9. Dean M. Glycogen in the uterus and fallopian tubes is an important source of glucose during early pregnancy. Biol Reprod. 2019;101(2):297-305.
10. Zawar MP, Deshpande NM, Gadgil PA, Mahanta AA. Histopathological study of endometrium in infertility. Indian J Pathol Microbiol. 2003;46(4):630-3.
11. Ikeme ACC, Ezegwui HU. Histological analysis of endometrial curettings performed for infertility in Nigeria. J Obstet Gynaecol. 2004;24(8):914-5.
12. Girish CJ, Kotur NS, Nagarajappa AH, Manjunath ML. A correlative study of endometrial glycogen content and other contributory factors on female fertility. Intl J Biomel Adv Res. 2012;3(1):30-5.
13. Kafeel S, Mushtaq H, Alam S. Endometrial histological findings in infertile women. J Islamabad Med Dental Coll. 2012;1(2):61-4.
14. Nandedkar SS, Patidar E, Gada DB, Malukani K, Munjal K, Varma A. Histomorphological Patterns of Endometrium in Infertility. J Obstet Gynecol India. 2015;65(5):328-34.
15. Kaur P, Kaur A, Suri AK, Sidhu H. A two-year histopathological study of endometrial biopsies in a teaching hospital in Northern India. Indian J Pathol Oncol. 2016;3(3):508-19.
16. Sharma V, Saxena V, Khatri SL. Histopathological Study of Endometrium in Cases of Infertility. J Clin Exp Pathol. 2016;6(2):1-3.
17. Murmu S, Baitha B. A Histopathological Study of Endometrium in Infertility. IOSR J Dent Med Sci. 2017;16(2):56-60.
18. Gupta A, Mathur SK, Gupta A. Co-orelation of histological dating and glycogen content by histochemical stain during various phases of menstrual cycle in primary infertility. Open J Pathol. 2013;3(2):65-8.
19. Pradhan SP, Dash A, Choudhury S, Mishra DP. A Study on Endometrial Morphology and Glycogen Content in Infertile Women. J Evid Based Med Healthc. 2017;4:528-31.
20. Gupta PL, Jethani M. Endometrial Glycogen - An Important Parameter of Infertility. J Obstet Gynaecol India. 1994;80:4-7.
21. Achalkar GV. Histopathological Study of Endometrium in Infertility. J Evol Med Dent Sci. 2018;7(24):2870-3.

Cite this article as: Shivappa P, Isaacs R, Mandrelle K, Goyal S. Glycopenic endometrium in infertility. Int J Res Med Sci 2022;10:1663-7.