Journal of Regenerative Biology and Medicine

ISSN: 2582-385X
Olimjanovna FM, et al., 2022- J Regn Bio Med
**Review Article**

# Glycadelin in Obstetrical Practice: Past, Present, Practice

**Fazilova Makhshura Olimjanovna[1*], Joel Isaias Osorio Garcia[2], Charles D. Sly[3] and Isabel Suarez Roman[4]**

[1]Samarkand state medical university, department of obstetrician and gynecologist, Republic of Uzbekistan, Samarkand

[2]Founder & CEO-Regenerage Clinic, USA

[3]Doctor of Pharmacy, JC Biotech LLC, USA

[4]Neonatologist. Universidad La Salle. Hospital Angeles Acoxpa, Mexico City

[*]**Corresponding Author:** Fazilova Makhshura Olimjanovna, Samarkand state medical university, department of obstetrician and gynecologist, Republic of Uzbekistan, Samarkand.

Received Date: 05-20-2022

Accepted Date: 05-30-2022

Published Date: 06-21-2022

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## Abstract

The article presents a review of the literature on one of the main proteins of the human reproductive system-glycodelin. The issues of the discovery of glycodelin, the features of synthesis, different names of the protein, its functions are covered. Depending on the place of origin, the same protein skeleton is glycosylated differently, giving rise to glycodelin isoforms with different biological effects. Glycodelin A (endometrial) and F (follicular fluid) inhibit the binding of spermatozoa and zona pellucida, thereby exhibiting contraceptive properties. In contrast, glycodelin C (cumulus) stimulates the binding of spermatozoa to the zona pellucida. Glycodelin S of seminal vesicles does not have a contraceptive effect, it affects the stability of the spermatozoa membrane, controls capacitation. The pronounced immunosuppressive activity of glycodelin A contributes to successful implantation and placentation, glycodelin S promotes the formation of antisperm immunity. The role of glycodelin in human reproductive function, the pathogenesis of reproductive losses (miscarriage, ectopic pregnancy, stillbirth), assessment of the functional state of the ovaries, fallopian tubes and endometrium, the maternal part of the placenta, and sperm fertility are shown. The review reflects both fundamental scientific data and the results of clinical studies of glycodelin content in menstrual blood, peripheral venous blood in women and semen in men, which made it possible to develop methods for diagnosing and predicting disorders of reproductive health and reproductive function in a married couple.

Further prospects for the study of glycodelin in science and practice are determined.

**Keywords**: Glycodelin; Placenta; Ovaries; Fallopian tubes; Endometrium; Seminal vesicles; Fertility.


**Citation:** Olimjanovna FM, Garcia JIO, D. Sly C, Suarez Roman I. Glycadelin in Obstetrical Practice: Past, Present, Practice. J Regen Biol Med. 2022;4(3):1-8.
**DOI:** https://doi.org/10.37191/Mapsci-2582-385X-4(3)-112

## Introduction

In women, glycodelin is synthesized in the ovaries (follicle, corpus luteum), fallopian tubes, secretory endometrium, maternal part of the placenta, and in men, in the seminal vesicles [1]. By the immunoperoxidase method, glycodelin was found in the ciliated and secretory epithelium of the mucous membrane of all sections of the fallopian tubes. Its content in the fimbrial region is higher in the secretory phase of the cycle [2]. Glycodelin was found in preovulatory and atretic ovarian follicles of fertile women, primordial follicles of the fetal ovary [3]. Glycodelin is found in menstrual blood and endometrial tissue extracts. In the endometrium of the proliferative stage, glycodelin, according to the method of immunodiffusion analysis, is absent [4]. In men, glycodelin was found in sperm plasma, seminal vesicle tissue (epithelium) and was not found in testicular, epididymis, and prostate extracts [4,5].

Meanwhile, the detection of mRNA encoding glycodelin in epithelial cells of the epididymis, prostate, ampullar part of vas deferens, as well as in spermatogonia and spermatocytes of the convoluted tubules of the rat testis suggests that all glandular formations of the male genital tract are able to participate in the synthesis to one degree or another. secretion of this glycoprotein [6]. Glycodelin has been found in endometriosis foci, extracts of malignant and benign tumors of the ovaries and uterus [7,8]. Apparently, it is impossible to recognize glycodelin as a strictly specific protein of the human reproductive system. Already at the very beginning of the study of this problem, there were reports of finding glycodelin in isolated cases in the bone marrow, mammary gland, breast cancer, pancreatic cystadenoma, hydradenoma, and parabronchial excretory glands [1].

Glycodelin has 3 main isoforms that are found in different tissues and environments of the reproductive system, depending on the place of their production: amniotic fluid (glycodelin A), endometrium (glycodelin A), seminal plasma (glycodelin S) and follicular fluid (glycodelin F). Depending on the place of origin, the same protein skeleton is glycosylated in different ways, giving glycodelins with different biological effects. Glycodelin A, derived from human endometrium, consists of unique lacdiNAc oligosaccharide sequences, and inhibits the binding of the sperm to the egg, thereby exhibiting contraceptive properties. In addition, this isoform of glycodelin modulates the endocrine function and differentiation of trophoblast cells [9]. In contrast, glycodelin S from seminal vesicles does not have such oligosaccharide sequences and has no contraceptive activity [10]. Follicular fluid glycodelin is a differentially glycosylated isoform of glycodelin, which, like glycodelin A, effectively inhibits the interaction of human spermatozoa and oocytes [11]. In the female reproductive tract, spermatozoa are exposed to glycodelin A and F, which inhibit the binding of spermatozoa and the zona pellucida.

As sperm cells migrate through the cumulus matrix, glycodelin F as well as glycodelin A-dependent inhibitory activity of gamete interaction is reduced due to the presence of a specific isoform of cumulus glycodelin,


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designated as glycodelin C, which has the effects of stimulating sperm binding to the zona pellucida [12]. It is assumed that glycodelin belongs to the family of microglobulin proteins that perform transport functions and bind biologically active molecules, primarily steroid hormones, with their subsequent transfer into cells by the so-called autocrine pathway [1]. Glycodelin is able to stimulate the production of chorionic gonadotropin by trophoblast cells [3]. There was a concept that glycodelin is a specific fertility phospholipase A2, the function of which is to catalyze the reaction that triggers and limits the synthesis of prostaglandins of all classes [4].

Glycodelin and an extract of decidual tissue containing a large amount of this protein have been found to have immunosuppressive activity [5]. The immunosuppressive effect of glycodelin A on the endometrium, which is necessary for implantation and maintenance of pregnancy, may be due to inhibition of the synthesis of interleukins (IL-1 and IL-2), as well as a decrease in the activity of normal killer cells [6,7]. Interacting with the CD45 membrane molecule, glycodelin causes apoptosis of T-lymphocytes, especially Th1, which can shift the balance of helpers towards The and contribute to the development of normal pregnancy [4]. Thus, the expression of glycodelin in the decidua during pregnancy regulates the depth of trophoblast invasion and is involved in successful implantation [4].

The study of the effect of glycodelin on the immunoregulatory cells of pregnant women in experiments in vitro showed that the development of threatened miscarriage in the early and late periods is accompanied by a decrease in the ConA-induced activity of lymphocytes. After incubation of immunocompetent cells with glycodelin, an increase in their activity was noted [1].

In experiments in vitro, glycodelin is able to reduce the functional activity of peritoneal macrophages. One of the main functions of glycodelin S is the regulation of the process of capacitation of spermatozoa. Glycodelin S of seminal plasma maintains spermatozoa in a non-capacitated state, being a factor blocking capacitation during their passage through the cervical mucus [9]. Glycodelin S realizes its effects by controlling the aggregate state of spermatozoa membranes, suppressing the release of cholesterol from them [2]. The weakening of glycodelin supervision in the chain "albumin-cholesterol-membrane viscosity-capacitation" is one of the attributes of overripe or "old" spermatozoa. Insufficiency of glycodelin in sperm means not only pseudocapacitation, but also the difficulty of sperm penetration into the egg, and if it occurs against this background, in most cases numerous pregnancy complications occur [3,8].

The relationship between an increase in the amount of antisperm antibodies in the blood serum of women with a decrease in the level of glycodelin has been proven in the spermatozoa of their spouses. It is possible that sperm glycodelin functions as an immunosuppressive protein in the formation of antisperm immunity in women [4]. There is also an opinion that the deficiency of glycodelin that develops with infertility of unknown origin indicates a failure of the “friend or foe” system, as a result of which the spermatozoon can be perceived by the egg as a foreign cell [5]. There is evidence of the regulatory effect of glycodelin on the mobility


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of male gametes. In ejaculates with oligozoospermia, the addition of glycodelin enhances gamete motility [6].

Conducted for more than 40 years, clinical studies by domestic and foreign authors clearly demonstrate the relationship between the level of glycodelin in biological fluids and reproductive health, human reproductive function, and methods for diagnosing and predicting reproductive disorders developed using glycodelin have found their application in obstetric and gynecological practice.

**Determination of glycodelin in peripheral blood**

The secretion of glycodelin into the peripheral blood in men and non-pregnant women is carried out in small amounts and is associated with their age. In women of childbearing age, there is a fairly noticeable variation in glycodelin levels (from 14 to 113 ng/ml). In menopausal women and men older than 60 years, the level of glycodelin in the blood is sharply reduced [7]. The content of glycodelin in the blood serum of healthy young non-pregnant women depends on the phase of the menstrual cycle: it increases in the secretory phase and 5 days before menstruation exceeds the protein level in the proliferative phase by 1.5–2 times [9]. During anovulation, the secretion of glycodelin is monotonous, its content in the peripheral blood of women does not change throughout the entire menstrual cycle [9].

In the peripheral blood, glycodelin is secreted from the endometrium in small amounts, determining the increase in the basic level of the protein in the 2nd phase of the menstrual cycle. Since the increase in the content of glycodelin in the venous blood serum in the 2nd phase is due to the intake of protein not only from the endometrium, but also from the fimbrial part of the fallopian tubes, measuring the level of glycodelin in the peripheral and menstrual blood makes it possible to indirectly assess the secretory activity of the fallopian tubes. With a normal level of glycodelin in the menstrual, but reduced-in the peripheral blood, one can probably judge the reduced secretory activity of the fimbrial tubes. In secondary infertility, there is no rise in the level of glycodelin in the 2nd phase of the cycle, which is probably associated with a decrease in the production of this protein in the fallopian tubes (fimbrial region) and endometrium, both due to their organic pathology and a violation of the hormonal activity of the gonads [1].

In women with early miscarriage, the content of glycodelin in the periovulatory period is reduced. With stillbirth and the birth of children with gross congenital malformations in history, the level of glycodelin is reduced both in the 1st phase of the cycle and in the periovulatory period, which may reflect dysfunction of the granulosa tissue and adversely affect the development of the follicle, delay ovulation and thereby lead to "aging" of the egg. In women with recurrent miscarriage and infertility of unknown origin, there is a decrease in the glycodelin content in the peripheral blood during the “implantation window” [1,8].

In patients with a common form of endometriosis, the content of glycodelin in the blood serum from the 5th to the 20th day of the cycle is higher compared to that in minor forms of pathology. In the dynamics of treatment, the elevated level of this protein in women decreases [9].


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**Determination of glycodelin in the follicular liquids**

The determination of glycodelin in the follicular fluid showed an inverse correlation between the level of glycodelin F in the follicular fluid and the number of high-quality embryos on the 3rd day after fertilization, which may be one of the factors affecting the competence of growing oocytes and the quality of the subsequent development of the embryo in vitro [5].

Extensive screening using enzyme immunoassay revealed elevated serum levels of glycodelin in patients with malignant processes of various localization, including malignant tumors of the ovaries and uterus in patients with melanoma non-small cell lung cancer and malignant pleural mesothelioma [2-5,8]. It has been shown that patients whose tumor expresses glycodelin have a greater chance of a positive disease outcome than patients with a tumor that does not express glycodelin [10]. Domestic scientists have studied the possibility of using glycodelin as a potential tumor marker in screening studies of patients at risk for cancer using a biosensor based on a composite of nanogold and glycodelin-specific immunoglobulins [12].

**Determination of glycodelin in endometrial scraping and menstrual blood**

The highest level of glycodelin in the endometrium is noted in the late secretory phase [10]. This protein is detected from the 19th–21st day of the menstrual cycle in the epithelial cells of the glands of the functional layer of the endometrium with maximum immunostaining at the end of the luteal phase [11]. The first appearance of glycodelin in the endometrium is observed 3 days after the release of luteinizing hormone (LH), on the $5^{th}$-$6^{th}$ day its concentration increases significantly when the "implantation window" opens [11].

In non-pregnant women, glycodelin in immunodiffusion analysis is determined not only in the secretory endometrium, but in the same amount in menstrual blood during ovulatory menstrual cycles [12]. In women with anovulatory menstrual cycles, acyclic uterine bleeding, and those taking hormonal contraceptives, glycodelin in menstrual blood is not identified in immunodiffusion [13].

Diagnostic criteria for the functional state of the endometrium were determined by examining the level of glycodelin in menstrual blood.

At the level of glycodelin from 16 to 64 μg/ml, a complete secretory transformation of the endometrium is determined, at values from 2 to 12 μg/ml-insufficiency of the luteal phase, below 2 μg/ml-anovulation, and at values from 128 μg/ml and above-the former in the pregnancy cycle. In the presence of pregnancy, the content of glycodelin in the blood from the uterine cavity depends on the duration of pregnancy and is higher in cases of artificial termination of pregnancy compared to spontaneous, which is due to the state of the decidual tissue [1,14]. The diagnostic criteria developed by us for the level of glycodelin in menstrual blood are currently used as standards in immunochemical kits for the determination of this protein (in terms of ng/ml).

Fertile women are characterized by a positive trend in the content of glycodelin in the


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peripheral blood during the menstrual cycle with an increase in the level of protein in the 2nd phase and high (16-64 μg/ml) values in the menstrual blood, characterizing the normal function of the ovaries and an adequate receptor response of the endometrium to progesterone. Meanwhile, data on the level of glycodelin will allow us to conclude that in fertile women who do not use hormonal contraception, there are cycles with luteal phase insufficiency (LFP) (16.7%), anovulation (16.7%), as well as with conceptions and subclinical spontaneous abortions (10%). It is subclinical abortions that probably determine the presence in fertile women of menstrual cycles with anovulation and NLF, which often follow the cycle of an aborted pregnancy [11].

In women with impaired reproductive function, primarily with early miscarriage, low levels of glycodelin in the endometrium is an important pathogenetic factor in spontaneous abortion. A low level of glycodelin in the menstrual blood reflects its reduced secretion in the endometrium and is determined in most women with repeated spontaneous pathological abortions of early pregnancy and in cases of birth of children with severe perinatal pathology [12].

It is assumed that an increased level of glycodelin A in the endometrium may be a predictor of implantation success. This assumption is supported by the fact that the contraceptive effect of emergency contraception with levonorgestrel (LNG) is partly determined by the change in glycodelin production.

The use of LNG as an emergency contraceptive before the LH peak leads to disruption of the secretion of glycodelin by the endometrium during the "fertile window" and in the luteal phase of the cycle with suppression of the immunosuppressive state in the uterus during implantation.

Determination of glycodelin in menstrual blood is recommended for screening women in preparation for an assisted reproductive technology (ART) program (IVF and embryo transfer). A low level of glycodelin in menstrual blood was found in patients with inflammatory diseases of the endometrium, uterine fibroids subject to surgical treatment in girls with hypothalamic syndrome of puberty, which reflects reduced receptivity and functional (secretory) activity of the endometrium [1].

**Glycodelin and its future**

Considering the large volume of clinical studies conducted with the proven diagnostic significance of glycodelin determination in various biological media, the technical simplicity and availability of analyzes (including cost), we believe that in the future it is possible to include these tests in the protocols and clinical recommendations of obstetrics and gynecology and services, primarily related to preconception preparation. Promising is the development of express methods for determining the level of glycodelin in semen and menstrual blood in the form of test strips. The development of drugs based on glycodelin to restore human fertility and maintain pregnancy may become important for practice.

**Conclusion**

Solving the issues of demography and the health of newborn children is associated with


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the reproductive health of married couples, so any research in this direction will have an important medical, socio-economic and state character. The history of the study of the human reproductive system protein glycodelin, starting from its discovery by domestic scientists Yu S Tatarinov and DD Petrunin to this day, is a vivid example of how a new substance in its value has become one with the classical regulators of the human reproductive system and is acquiring a high rating as a diagnostic marker of many pathologies.

Core of many pathologies. Summarizing the knowledge accumulated to date about glycodelin, it can be stated that this glycoprotein plays a significant role in the functioning of the reproductive system of both women and men. This protein regulates the processes of reproduction of offspring at the stages of gamete migration along the genital tract and activation of the acrosomal reaction, participates in the course of normal pregnancy, in the development of its complications and perinatal pathology. This knowledge has already made it possible to use glycodelin as an indicator of the functional state of the reproductive system and a diagnostic marker of pregnancy complications. Associated with many oncological diseases, glycodelin at the present stage is one of the candidates for testing and monitoring the effectiveness of the treatment of tumor diseases. Given the variety of functions of this glycoprotein, including contraceptive properties, the scope of its application in medicine can be expanded.

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