

Causes of Infertility in Women with Diabetes: Literature Review

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Abstract:

Diabetes Mellitus (DM) is a serious chronic disease, resulting from long-term hyperglycemia can lead to various complications. Complications of DM are associated with changes occurring in blood vessels and nerve fibers.

Diabetes can affect a woman's reproductive function and lead to infertility. Decreased fertility in women with DM can be caused by various factors related to this disease. To date, the final mechanisms of reduced reproductive function in these women have not been fully elucidated, but it is known that the leading role belongs to chronic hyperglycemia.

Purpose: Based on these literature sources, to investigate the possible causes of infertility in women with diabetes.

Object: reduced fertility in women as a result of diabetes.

Research methods: a review of literary sources.

Results: There are quite a few causes of infertility and reduced fertility in women with DM, these include complications of diabetes (diabetic polyneuropathy); insulin resistance and, as a result, polycystic ovary syndrome; obesity; autoimmune and genetic factors; disorders of the menstrual cycle and hormone balance; low quality of egg cells due to oxidative stress and the formation of glycation products; reduction of cervical mucus due to hormonal disbalance, dehydration and inflammatory processes of the genital organs; psychogenic factors (phobias, fear of childbirth, future changes both in the body and in life).

Conclusions: Based on the study of literary data, it can be said that the main causes of infertility in women with DM are caused by chronic hyperglycemia, and as a result, the development of pathological conditions that lead to disorders in the reproductive system. In addition, the causes of infertility in women with DM include disorders of the menstrual cycle and hormone balance, polycystic ovary syndrome, obesity, and autoimmune and genetic mechanisms. Taking this into account, glycemic control, prevention and treatment of diabetes complications, lifestyle modification, nutrition, and psychological health support are necessary.

Key words: infertility; diabetes in women; insulin resistance; hyperglycemia

Introduction

Infertility, as defined by the WHO, is the absence of pregnancy during a year of regular sexual life without the use of contraception (for persons aged 35 and older - within six months). It is believed that pregnancy occurs with regular (2-3 times a week) intercourse within 1 year in 75% of married couples who do not use contraceptives. Infertility affects millions of people – and affects their families and communities. According to WHO estimates, approximately one in six people of reproductive age worldwide will experience infertility during their lifetime. [World Health Organization (WHO). International Classification of Diseases, WHO 2022]. In recent years, WHO has recognized infertility as a disease of women and men.

From a modern point of view, infertility in most cases can be caused by several reasons, both on the part of the woman and on the part of the man,

or both together. One part of these causes are congenital disorders, the other is traumatic, infectious, hormonal, neuro-vascular, metabolic, and others. That is, the onset of pregnancy must be preceded by numerous processes that flow normally: oogenesis and ovulation, penetration of the egg into the fallopian tube, its fertilization, segmentation and transport of the egg, implantation in the endometrium, processes of spermatogenesis, sperm ejection and its deposition in the vagina, penetration of spermatozoa into the uterus and fallopian tubes. The presence of an obstacle on any segment of this long path can lead to impaired fertility and infertility [32,19,16,52].

Analysis of literary data

Infertility occurs in 10-15% of all marriages. Female - in 55-60% of cases, male - in 40-45%. Infertility negatively affects the birth rate and often causes a breakdown in family relations.

In a systematic review devoted to the study of female and male infertility and infertile couples, published in the journal "Jurnal Kebidanan" in 2022, the authors decided to identify the determinants of infertility, based on the analysis of studies from 8 national and international databases. According to the systematic review, 4 main determinants of infertility were identified, namely: history of reproductive disorders, prevention of infertility, solving problems, mental readiness of the couple, and lifestyle of the couple. These factors are the most widely studied in research, among the factors that affect infertility, it is found that research on the mental readiness of couples can be prepared as early as possible, even before marriage. In infertility problems, all couples need to understand the points of support and ways to deal with mental health problems [54].

There are several classifications of infertility, according to which they distinguish: female, male, or combined; primary or secondary; absolute or relative. By etiology, they distinguish endocrine, tubo-peritoneal, immune, infertility caused by cervical factors, and infertility caused by uterine factors.

Other forms of infertility include mixed, psychogenic, and infertility due to infantilism and hypoplasia of internal genital organs [32,19,16,52].

That is, the causes of infertility can be different, conditionally they can be divided into physiological and psychogenic.

Infertility and its probable causes in women without diabetes fallopian tubes, endocrine system, and others. Fertility can also be affected by the age of future parents.

Etiology of female infertility:

- endocrine factors - 35-40%;
- tubular and peritoneal factors - 20-30%;
- immunological factors – 20%;
- cervical factor - 5%
- in approximately 10-15% of cases, the cause of infertility remains unexplained [32,19,16,52]

Endocrine factors

Hormonal or endocrine disorders that provoke infertility can be associated with ovarian diseases. In other, more rare cases, a woman cannot become pregnant due to dysfunction of the adrenal glands, thyroid gland, and pituitary gland. With these diseases, there is a violation of the ovulation mechanism and mature egg cells do not leave the follicle.

their absence, increased production of male sex hormones, menstrual cycle disorders, problems with conception, and ovulation rarely occurs [40,47].

Pathology of the uterus and its appendages

In these cases, there are several reasons for impaired fertility. First of all, this is a mechanical obstacle. The formation of adhesions in the fallopian tubes after the transferred inflammation and violation of their patency, covering the ovaries with adhesions leads to the fact that, as a result, the mature egg cannot penetrate into the fallopian tube.

Among the causes of infertility in women, it should also be mentioned the removal of fallopian tubes, due to the occurrence of ectopic pregnancy and infectious processes of the uterus. Infectious processes of the uterus that can cause fertility disorders include endometriosis.

Endometriosis is the growth of the mucous membrane of the uterus inside other organs outside of it. According to the WHO, approximately 10% of women of reproductive age worldwide suffer from endometriosis. [World

Health Organization (WHO). International Classification of Diseases, 11th Revision (ICD-11) Geneva: WHO 2018]

The causes of reduced fertility include pathologies that prevent embryo implantation - scars on the walls of the uterus after surgical treatment, endometritis (inflammation of the upper layer of the mucous membrane of the uterus), myoma (benign tumor), hyperplasia, and polyps [38,28,31].

Immunological infertility

The immunological reason is related to the presence of anti-sperm antibodies in the female body. Protein compounds perceive sperm as a foreign body and the immune system tries to destroy them. Fertilization itself becomes impossible. If this happens, then the probability of implantation of the embryo is reduced to a minimum. Such a pathological process can develop due to frequent spontaneous abortions [31].

Age factor

Women are born with a certain number of egg cells in their ovaries. On average, one egg matures per month. The exception is long-term treatment with sex hormones, and functional disorders of the reproductive system when several eggs are ready for fertilization. Over the years, the chance of conceiving a child decreases. At the same time, ovulation is observed every month, but the egg does not reach maturity. With age, the so-called process of "ovum aging" starts. The reason is chromosomal aberrations that block fertilization, lead to disturbances in the physical development of the embryo, as a result of which it becomes non-viable, and spontaneous abortion may occur [40,47,25].

Infertility in women with DM

Decreased fertility in women with DM can be influenced by various factors associated with this disease. To date, the final mechanisms involved in reproductive dysfunction in women with DM have not been fully elucidated, but it is known that the leading role belongs to chronic hyperglycemia.

As the studies show, diabetes causes considerable oxidative stress in females, which leads to DNA damage. DNA damage causes cell cycle arrest and cell death, preventing the development of oocytes [35]. Hyperglycemia is regarded as one of the major causes of DM-induced complications by activating a range of damaging pathways that appear to be initiated by mitochondrial superoxide overproduction. Transient episodes of hyperglycemia produce tissue damage through processes requiring recurrent acute alterations in cellular metabolism [55] It is well acknowledged that proper diabetes management, namely glycemic control, is critical in minimizing, preventing, or mitigating diabetic complications [46].

So, the possible causes of impaired fertility in women with DM will be discussed further in this article.

Disorders of the menstrual cycle and hormone balance in women with DM.

Disorders of the fine balance of estradiol, testosterone, and progesterone in the body of a woman with DM can cause menstrual cycle disorders, infertility, polycystic ovary syndrome, etc. [57].

Some studies suggest that women with DM have higher testosterone and lower estradiol compared to women without diabetes. This suggests that DM may be associated with a disbalance of sex hormones.

Studies show that high testosterone levels are associated with increased insulin resistance, hyperinsulinemia, and obesity in patients with type 2 diabetes.

On the other hand, excess insulin stimulates an increase in androgen levels by inhibiting the release of the sex hormone-binding globulin, a protein

from the liver, which is responsible for transporting testosterone in the blood.[57]

Progesterone is an important hormone for fetal survival and pregnancy maintenance. Elevated levels of progesterone during pregnancy can lead to the development of insulin resistance and gestational diabetes. In non-pregnant women, elevated levels of progesterone can be observed with ovarian cysts, hyperplasia of the adrenal glands, and ovarian cancer [57].

Cortisol is another hormone that affects blood sugar levels. Cortisol is normally produced by the adrenal glands every day to help the body cope with stress. During times of stress, the body produces more cortisol, which raises blood sugar levels so that the body has enough energy. In the long term, high cortisol levels contribute to insulin resistance and, as a result, hyperglycemia [57].

Persistently high cortisol levels are characteristic of women with PCOS. The presence of hormonal disorders in a woman with DM significantly worsens the course of diabetes and increases the risk of developing diabetic complications [57].

Polycystic ovary syndrome (PCOS) in women with DM as a cause of infertility

Despite the progress in medicine, the large amount of scientific and popular scientific literature, availability of Internet resources, the number of patients with PCOS in the world is constantly growing. In 2022, the results of an analysis of the prevalence of PCOS in 204 countries from 1990–2019 were published, the number of patients increased by almost 30% since 1990 [13]. The increasing incidence of this syndrome is associated with the increasingly common DM and disorders of insulin and glucose metabolism, as well as with the epidemic of obesity and oxidative stress associated with a sedentary lifestyle and excessive intake of simple sugars in the diet [45].

The etiology of PCOS is multifactorial. The disorders that occur in this endocrinopathy are the result of a complex interaction of genetic, epigenetic, gender, racial, environmental, and other factors. PCOS affects not only the reproductive system but also the entire body and accompanies the patient throughout his life [1,17,18,29,44,45,50].

PCOS occurs under the conditions of insulin resistance and subsequent hyperinsulinemia, which, together with an increase in the level of luteinizing hormone, affects the theca cells of the ovaries and leads to an increase in the production of androgens. The increased level of androgens interferes with the normal maturation of follicles, causing infertility. Hyperinsulinemia often leads to type 2 diabetes and metabolic syndrome, increasing the risk of cardiovascular disease. In patients with type 2 DM, regular glycemic control and screening for cardiovascular risk factors, including measurement of blood pressure, waist circumference, BMI, and lipid profile, are important in addition to addressing fertility issues associated with PCOS. [5,8,9,11,13,24,49,53]

Obesity as a cause of infertility in women with DM type 2

DM type 2 and obesity are interrelated and have an impact on women's reproductive health. The common basis in both cases is insulin resistance, under the conditions of which the regulation of hormones responsible for ovulation, such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH), is disturbed, as a result of which violations or even absence of ovulation may occur. Obesity and insulin resistance also affect the secretion of leptin, adiponectin, and other hormones, which also affect the reproductive system.

Excess adipose tissue in women increases the risk of subfertility for several reasons

The best-understood association between obesity and subfertility is ovulation versus anovulation [27]. Hormone dysregulation and a

combination of insulin-related disorders, low sex hormone binding proteins, and high levels of androgens play a role. In combination, these cause dysfunction of the hypothalamic gonadotropins hormone secretion, resulting in a reduction in the number of follicles as well as progesterone levels [27].

White adipose tissue is a secretory and storage organ with multiple functions [23]. By secreting cytokines, white adipose tissue plays a role in metabolism. One class of cytokines in particular, known as adipokines, has been linked with subfertility [23]. These include leptin, ghrelin, resistin, visfatin, chemerin, omentin, and adiponectin.[26] Abnormalities of these, or disruption in homeostasis, can affect cell function [23]. For example, high levels of adipose tissue in women exacerbate polycystic ovary syndrome due to increased levels of harmful adipokines and decreased levels of beneficial adipokines [26]. Receptors for adiponectin are expressed in reproductive tissues, predominantly in the ovaries, endometrium, and placenta. Reduced expression of these receptors has been linked to recurrent implantation failure [41].

Not only has decreased endometrial receptivity been linked to a decline in adiponectin, but the risk of diabetes increases because one of the roles of adiponectin is an uptake of glucose in the liver [23]. This impairs sensitivity to insulin, linking obesity to insulin resistance and type 2 diabetes mellitus. Chemerin, on the other hand, impairs follicle-stimulating hormone (FSH) secretion.

Ovarian follicles are also affected by obesity in other ways. Studies have shown that non-esterified fatty acid composition in follicular fluid is influenced by the process of lipolysis. [3] Furthermore, follicular fluid contains high levels of oleic acid in patients with high BMI and this can lead to embryo fragmentation.[41] When an embryo is in the blastomere stage, chemicals such as stearic acid (also found at elevated levels in follicular fluid of women with high BMI) can lead to poor blastomere score. In mice models, leptin-rich mice demonstrated impaired folliculogenesis, as well as impaired and reduced rates of ovulation, as leptin inhibits estradiol production by these granulosa cells, which are luteinizing hormone (LH) driven. Faster rates of apoptosis in granulosa cells were also seen [42].

Oocytes of women who are obese or overweight have lower levels of n-3 polyunsaturated fatty acids compared with oocytes of women with normal weight [21].

Obesity and the presence of adipose tissue have also been linked to increased amounts of inflammation in the body, and not only increase tumor necrosis factor (TNF) but also markers like C-reactive protein (CRP) and interleukin [10,20,21,30,39].

Low egg cell quality as a cause of infertility in DM

Low egg cell quality can be one of the causes of infertility in women with DM. Egg cell quality is a critical factor for successful conception and normal pregnancy. Oocyte quality in women with DM can be affected by various factors that develop as a result of hyperglycemia, including oxidative stress, formation of glycation products, changes in oocyte microtubules, endometrial changes, etc. [13].

Reduction of cervical mucus

Cervical mucus plays a critical role in fertility by facilitating sperm transport, protecting sperm from the acidic environment of the vagina, and providing an ideal environment for sperm survival and motility. When there is a decrease in cervical mucus, it can negatively affect a woman's ability to get pregnant.

Diabetes can cause a change in consistency and a decrease in cervical mucus. This may be related to hormonal imbalance and physiological changes in a woman's body, dehydration, and the presence of inflammatory processes in women with diabetes. High blood sugar in

diabetes can cause one to urinate more often, which can cause dehydration, which can reduce the production of cervical mucus, making it thicker. Chronic inflammation that occurs in women with DM can affect the glands of the cervix that produce mucus and lead to a decrease in its secretion [13].

Autoimmune factors as a cause of reduced fertility in women with DM

Women with DM may have an increased risk of autoimmune conditions that can reduce fertility by affecting the reproductive organs or preventing the implantation process.

As a result of autoimmune aggression, the body's immune system attacks its cells and tissues, causing inflammatory reactions and damage.

Autoimmune factors that can affect the fertility of women with DM include the following: autoimmune oophoritis, autoimmune endometritis, autoimmune thyroiditis, autoimmune dysfunction of eggs, and autoimmune implantation failure.

The exact mechanism by which autoimmune reactions affect fertility may be different for each woman and may vary depending on the type and severity of diabetes [13].

Diabetic polyneuropathy as a cause of female infertility

Diabetic polyneuropathy - a complication of diabetes that develops against the background of chronic hyperglycemia, can be one of the causes of infertility in women. Autonomic polyneuropathy of the pelvic organs in women has various manifestations and symptoms. These include: sexual dysfunction, decreased vaginal moisture, ovulation disorders, changes in the structure of the endometrium, and menstrual cycle disorders. The listed symptoms in one way or another affect not only the reproductive capacity but also the sexual activity and satisfaction of a woman [13].

Psychological or psychogenic factors

Psychological infertility occurs as a result of a woman's unconscious or conscious desire not to have children. This group includes patients with phobias, fear of childbirth, and future changes - both in the body and in life. Difficulties with pregnancy can be provoked by a woman's reluctance to give birth to a child from a certain man.

The negative psychological factors that create the risk of infertility include:

- somatization (psychological protection of the nervous system) of experiences, anxiety, and grief;
- regular stress, psycho-emotional overstrain;
- excessive control over one's own life;
- lack of awareness of one's femininity, and attractiveness;
- idealization of pregnancy and the role of parents;
- children's psychological injuries [2,6,7,12,22,34,36,43]

Hyperglycemia and its effect on fertility in women with DM

Chronic hyperglycemia, which can be the result of insufficient compensation of DM, non-compliance of the patient, or other reasons, affects not only the reproductive health of a woman but also all organs and systems. Chronic hyperglycemia leads to the development of complications of diabetes, deterioration of the quality of life, and reduction of its duration.

Based on the above, chronic hyperglycemia is the cause of complications of diabetes, negatively affects the reproductive capacity of women, leads to a decrease in fertility and increases the risk of pregnancy pathology and fetal malformations.

Some clinical studies have shown that improving glycemic control can increase the chances of pregnancy in women with diabetes. [56] In addition, other studies have shown that insulin treatment can help increase estrogen levels and improve reproductive function in women with diabetes.

However, to better understand the relationship between diabetes and infertility in women, additional studies involving a large number of patients are needed.

Several significant clinical studies have examined the relationship between infertility and diabetes in women. The main results of some of them are given below.

A 2017 study in China found that women with type 2 diabetes are more likely to carry a pregnancy with malformed fetuses. The study looked at more than 5,000 pregnant women, of whom 190 had type 2 diabetes. Women with type 2 diabetes had more cases of congenital heart, brain, and kidney defects in their newborns compared to women without diabetes [51].

A study published in the journal *Human Reproduction* in 2017 found a link between elevated levels of glycosylated hemoglobin (HbA1c) and reduced fertility in women with type 1 diabetes. The study involved 1,200 women with type 1 diabetes who tried to get pregnant. The results showed that women with higher HbA1c levels were less likely to conceive in the first year of trying, compared to women with lower HbA1c levels. In addition, elevated HbA1c levels were associated with increased rates of spontaneous abortions and cesarean sections. The study found that women with higher HbA1c levels had lower chances of conceiving and higher risks of refusing IVF procedures [33,37].

Results from a study in Nigeria showed that elevated HbA1c levels were associated with reduced antral follicle count and reduced free estradiol (E2) in women with type 1 diabetes. In addition, elevated HbA1c levels were shown to affect egg quality, which can lead to a decrease in the chances of successful conception. The study highlights the importance of controlling blood glucose levels in women with type 1 diabetes to improve their fertility and avoid other complications of diabetes [33,37].

A study published in the journal *Obstetrics & Gynecology* in 2017 found that women with type 1 and type 2 diabetes are more likely to experience amenorrhea and anovulation than women without diabetes. This study was based on a meta-analysis of 17 previous clinical trials that included women with type 1 and type 2 diabetes. The aim was to evaluate the effect of diabetes on fertility disorders in women.

As a result of studying the data, it turned out that women with type 1 and 2 diabetes are more likely to experience amenorrhea and anovulation, which can significantly complicate the process of conception and pregnancy. However, the study indicated that maintaining glycosylated hemoglobin below 7% may help reduce the risk of impaired fertility in women with both types of diabetes.

The study was based on data analysis of more than 10,000 women, aged 20 to 45, with DM type 1, DM type 2, and non-diabetic people. The results showed that women with diabetes were significantly more likely to experience fertility disorders, such as amenorrhea and anovulation, compared to women without diabetes. A particularly high incidence of impaired fertility was found in women with type 1 diabetes. The findings indicated that hyperglycemia may increase the risk of impaired fertility in women with DM type 1 and DM type 2 [56].

A study published in the journal *"Diabetes Research and Clinical Practice"* in 2018 established a link between insulin resistance and reduced fertility in women with DM type 2. The study was conducted on 78 women with DM type 2, who were divided into two groups: a group with insulin resistance and a group without it. The results showed, that women with insulin resistance had a significantly lower level of fertility.

The study found that women with insulin resistance were more likely to have anovulation and less likely to get pregnant compared to women without insulin resistance [4,48].

Another study, published in the journal *Reproductive Biomedicine Online* in 2017, found a link between decreased levels of melatonin (a hormone that regulates the circadian rhythm) and decreased reproductive function in women with DM type 2, 100 women with DM type 2 and 100 healthy women (control group) participated in the study. The study found that melatonin levels were significantly lower in women with type 2 diabetes who had fertility problems compared to women without diabetes. Also, a decrease in the concentration of estradiol and progesterone was found in women with DM. Additionally, lower melatonin levels have been linked to reduced egg cell quantity and quality in women with DM type 2, which can lead to reduced reproductive function and infertility. Thus, the study confirms the importance of regulating the circadian rhythm and melatonin level for preserving reproductive function in women with DM type 2 [15].

Prevention of infertility:

Considering the negative impact of hyperglycemia on the body of a woman with diabetes as a whole, on the development of complications of diabetes, and reduced fertility, the need to control glycemia and achieve the target of HbA1c and glycemia is obvious. Self-monitoring of blood glucose and body weight, healthy eating, and regular preventive examinations can help avoid complications of diabetes and infertility. In addition, there are general recommendations for maintaining the health of sexually active women that can improve reproductive function, including the following:

- Sex life with a permanent partner.
- Using condoms when having sex with a questionable partner.
- Regular preventive examinations at the gynecologist - 1-2 times a year.
- Immediate consultation with a doctor if symptoms of pelvic organ disease appear.

Conclusions:

Infertility is not only an individual problem of a specific family, but also a problem of society, therefore it is important to study its causes, prevention, and further treatment. Based on the study of literary data, it can be said that the main causes of infertility in women with diabetes are caused by chronic hyperglycemia, and as a result, the development of pathological conditions that lead to disorders in the reproductive system. In addition, the causes of infertility in women with diabetes include disorders of the menstrual cycle and hormone balance, polycystic ovary syndrome, obesity, and autoimmune and genetic mechanisms. Taking this into account, glycemic control, prevention and treatment of diabetes complications, lifestyle modification, nutrition, and psychological health support are necessary.

Solving the problem of infertility is complex. Couples facing infertility problems should receive counseling support. This is a vital intervention for the mental health of these people and allows them to express the problems they feel are related to their inability to have children, which can help in the comprehensive therapy of infertile couples.

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