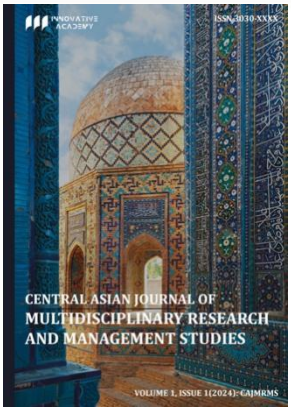

EARLY PREGNANCY LOSS: THE INFLUENCE OF ENDOGENOUS RISK FACTORS AND THEIR SIGNIFICANCE

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https://doi.org/10.5281/zenodo.14776476

ARTICLE INFO

Received: 27th Janyary 2025
Accepted:29th January 2025
Published:30th January 2025

KEYWORDS

include immune, genetic, anatomical, endocrine.

ABSTRACT

This paper examines endogenous risk factors that influence early pregnancy loss. The paper analyzes the biological, hormonal, genetic and immunological aspects that may contribute to pregnancy failure. Special attention is paid to endocrine dysfunctions, inflammatory processes and genetic mutations, as well as their impact on embryo development. Recommendations for diagnosis and management of risk factors to minimize the threat of pregnancy termination are presented.

INTRODUCTION

Despite the undoubtedly significant successes in solving the problems of reproductive dysfunction at the present stage, about 50% of conceptions in the population end in failure [1]. In the structure of reproductive losses, frozen (non-developing) pregnancy (FDP) occupies a special place, accounting for 10-20% [2]. A long-term delay of a dead fertilized egg in the uterus is associated with potentially dangerous hemostatic and infectious inflammatory complications that negatively affect reproductive function in the future [3]. As a rule, miscarriage (MP) is triggered by the combined effect of several factors, each of which may be insignificant, but together they can cause the death of the fertilized egg [4].

The main and well-studied causes of FDP include immune, genetic, anatomical, endocrine and infectious factors [3]. The generally recognized and most common factors of NT are chromosomal abnormalities and chronic endometritis [2, 5]. Moreover, the highest frequency of uteroplacental vasculopathy and chronic inflammatory reaction in the decidual tissue is observed in the first NT [6]. In this regard, NP in young primigravidas, not yet compromised by unfavorable factors, is of particular interest [7]. A thorough analysis and consideration of possible etiological factors and conditions that contribute to termination of pregnancy will reduce the risk of recurrence of reproductive losses and determine the tactics of management in the future [8]. The article pays special attention to endogenous factors caused by the characteristics of the female body, capable of creating unfavorable conditions for embryo development. Such factors can be clarified and, if possible, eliminated at the stage of pregravid preparation.

Infectious risk factor

Currently, the role of microbial factor and chronic endometritis is the leading mechanism of initiation of disorders of adequate development of the fetal egg or its death [5]. In the structure of the causes of early reproductive losses, infectious diseases occupy about 15% [14]. According to different data, the spectrum of opportunistic bacteria accounts for 20 to 67.7%, viral-bacterial associations - up to 70% [15]. It should be emphasized that

monoinfection is the causative factor in only 20% of cases, while in other cases the infection is mixed, representing various combinations of pathogens, including viruses [16]. In 2006, at the FIGO World Congress in Kuala Lumpur, the world community decided to consider every case of WP associated with chronic endometritis [17]. It should be noted that in 50% of women endometrial dysfunction is caused not by inflammation, but by the progressive syndrome of reconstructive plastic insufficiency, which results in atrophy of the uterine mucosa. This process in various tissues and organs, including the endometrium, is based on the depletion of regenerative potential [18]. This is manifested by a decrease in the number of protein synthesizing organelles in epitheliocytes, which causes atrophic changes with a decrease in secretory activity and expression of receptors for sex steroids [19].

Sexually transmitted infections, syphilis, and TORCH infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus) can increase the risk of early pregnancy loss [20]. However, HIV infection has no significant impact on pregnancy outcome and complications [21].

In order to prevent pregnancy loss due to infectious factors, the main objective is to diagnose urogenital infection and its timely treatment before the infectious and/or inflammatory process leads to irreversible changes in the cervix, myometrium, placenta, fetal membranes and fetus.

Anatomical factors

A special risk group for reduced fertility includes women with anomalies of uterine anatomy, the incidence of which ranges from 3.2 to 16.9% [22]. Uterine anomalies are usually divided into congenital and acquired, and in congenital uterine defects, late termination of pregnancy and habitual UB are more frequently observed. Congenital defects as causative factors of non-pregnancy include genital infantilism and uterine malformations: bicornuate uterus (37%), partial or complete intrauterine septum (22%), saddle-shaped uterus (15%). Acquired anatomical defects include the following: intrauterine synechiae, Asherman syndrome (AS), uterine myoma, endometrial polyp, and isthmic cervical insufficiency [23]. Thus, bicornuate uterus as a causative factor of NB occurs in 2-37% of cases, while submucosal myoma is considered a risk factor for fetal loss in 8% of cases [24].

Mechanical trauma to the basal layer of the endometrium mainly in pregnancy-related situations, such as cervical dilatation, curettage of the uterine cavity wall during NB, and in the postpartum period, is considered to be the leading etiologic factor of CA syndrome [25]. Only the combination of such symptoms as decreased fertility, hypo- and amenorrhea, abnormal placentation in the history, spontaneous miscarriages, and the presence of synechiae at hysteroscopy allows the term “Asherman syndrome” to be used.

Endocrine risk factors

Endocrine factors play a leading role in the genesis of NB and are registered on average in 17% of patients with reproductive losses, although there is data on a higher frequency of endocrine disorders, in some groups - up to 68.5% [12]. A special place is given to hyperandrogenic conditions: polycystic ovaries and congenital dysfunction of the adrenal cortex, the prevalence of which in the population is quite high 6-21% [20]. Elevated testosterone levels are naturally associated with hypoestrogenism and the formation of luteal phase insufficiency in the future. In addition, its elevated level reduces the contractile activity of the myometrium, contributing to the retention of the ovum [29]. According to literature data, every second pregnancy in patients with hyperandrogenism of various genesis is terminated in the first trimester, and in every third woman - by the type of embryo death, in every fourth case anembryony is recorded [30]. In addition, every second patient with polycystic ovary disease is overweight or obese, in 30-70% of patient’s insulin resistance is recorded, which has an extremely unfavorable effect on the outcome of pregnancy [31].

Thyroid diseases are highly prevalent in the population (10–26%) and can have a negative impact on the course and outcome of pregnancy [32]. Thus, reproductive losses in

the absence of correction of functional disorders of the thyroid gland are 57.3% versus 2.2% in women without them. In this case, pregnancy losses are mainly registered as type IUGR and occur in the first trimester of gestation (80.1%) [33]. Autoimmune thyroiditis and primary hypothyroidism are risk factors for termination of pregnancy due to a decrease in the stimulating effect of thyroid hormones on the function of the corpus luteum, which plays a major role in maintaining pregnancy in the early stages [34]. In addition, the presence of antibodies to thyroid peroxidase can increase the risk of pregnancy loss and can be considered as a marker of autoimmune dysfunction [35].

Recently, diabetes mellitus has been considered a possible causal factor in the development of BC, which is most likely associated with the toxic effect of ketoacidosis on the developing embryo [8]. Obesity is a global problem throughout the world, with 30-60% of women of reproductive age being overweight and 25-27% being obese [9]. According to the latest estimates from the World Health Organization, by 2025, obesity is expected to develop in 50% of women on our planet. Pregnant women with obesity have a higher risk of early loss of the ovum than women with normal body weight due to the fact that obesity is accompanied by high comorbidity and contributes to BC.

Immunological factors

In 50-80% of cases with a normal fetal karyotype, the causes of early reproductive losses may be immunological factors that play an important role in the processes of fertilization, implantation and placentation. Immunological disorders may concern both humoral (antiphospholipid syndrome) and cellular immunity, where the HLA system (human leukocyte antigen), being a highly polymorphic gene locus, controls the interactions of all immunocompetent cells of the body, including the recognition of its own and foreign, as well as altered own cells [11]. The initiation and implementation of the immune response of HLA class I genes inhibit the NK cell receptor (natural killer), which helps to reduce the immune response at the mother-fetus border, thereby ensuring immune tolerance to the fetus and a protective effect at all stages of implantation. A special role in the success of pregnancy is played by the expression of the HLA-E, HLA-C and HLA G genes, which are expressed tissue-specifically by the cells of the cytotrophoblast, placenta and amnion, influencing the development of pregnancy complications, namely, early fetal loss [4]. In turn, with a normal fetal karyotype, an important role in the pathogenesis of anembryony is given to leukocyte antigens HLA-E (human leukocyte antigens E) and NK lymphocytes. It has now been established that an imbalance in the epigenetic regulation of immunocompetent cells can affect the processes of acetylation, phosphorylation or methylation of histone proteins expressing the genes of pro-inflammatory cytokines. It is known that prolongation of pregnancy is due to the balance of pro- and anti-inflammatory cytokines.

The Th-1 response is characterized by the activation of macrophages under the influence of type 1 helpers with an increase in their bactericidal potential, which is accompanied by the activation of proinflammatory cytokines - interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α), interleukins: IL-2, IL-12, IL-1, IL-8. The role of Th-1 cytokines in NB is explained by the embryotoxic effect of IFN-γ and TNF-α. Cytotoxic and cytostatic effects on the trophoblast are lethal and lead to premature termination of pregnancy [25]. NB is characterized by a statistically significant decrease in the level of IL-4, IL-8 and interferon-α compared to the norm against the background of an increase in the concentration of TNF-α and IFN-γ [2]. Excessive increase in the level of proinflammatory cytokines has a direct embryotoxic effect, disrupts placentation processes, which can lead to thrombosis and ischemic necrosis in the placenta. As a result, their interactions in the endometrium form a pathological type of immune response to trophoblast antigens, resulting in a cascade of reactions leading to NB [7]. It is believed that proinflammatory cytokines produced by macrophages (TNF-α, IL-1, IL-6, IL-8) stimulate the synthesis of prostaglandins, thereby enhancing the contractile activity of the myometrium, contributing to unfavorable gestation

outcomes [28]. In turn, with a favorable pregnancy, the cytokine balance shifts towards immunosuppressive Th-2 cytokines (IL-4, IL-10, TGF-β), inhibiting cellular immune responses and stimulating steroidogenesis (progesterone, chorionic gonadotropin), as well as the production of blocking antibodies. At the same time, inhibition of IL-10 production in the early stages, on the contrary, causes termination of pregnancy [19]. Almost 10% of cases of spontaneous abortion are associated with systemic autoimmune conditions leading to the development of antiphospholipid syndrome (APS). Pathophysiological processes in spontaneous abortion in patients with APS may be associated with inflammation of the chorion/placenta, disruption of normal trophoblast function, and prothrombotic phenomena [20]. Disturbances in the immune status in spontaneous abortion may be due to secondary immunodeficiency provoked by various unfavorable factors. Among them, the most significant are bacterial infections, stress, non-specific chronic diseases, long-term use of drugs and radiation [26]. A study of the gravid endometrium in young women with NT in the first trimester established the presence of clinically significant expression of leukemia inhibitory factor (LIF) molecules along with increased expression of the angiogenesis marker CD34 in comparison with those in women of older reproductive age [27]. Moreover, the development of NT is equally possible both against the background of incomplete gravid transformation of the endometrial stroma and with its complete transformation, and regardless of the intake of hormonal drugs aimed at maintaining pregnancy [28].

Conclusion

The problem of early reproductive losses remains one of the most important and currently unresolved. In 80% of cases, early reproductive losses are caused by chromosomal abnormalities or malformations. The causes of other reproductive losses are little-known exogenous or endogenous factors, the study of which seems to be a resource measure capable of influencing the outcome of pregnancy, especially the first, the termination of which increases the risk of developing an unfavorable outcome of the subsequent gestation with the formation of the syndrome of "habitual fetal loss". Thus, the currently available information demonstrates the diversity of factors underlying the pathogenesis of non-developing (frozen) pregnancy, which requires further study and development of an individual approach at the stage of pregnancy planning. Forecasting is based on the study of unfavorable factors and the definition of a high-risk group for early reproductive losses. In turn, their prevention is determined by a set of measures aimed at eliminating individual risk factors at the pregravid stage.

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