Original Article

ISSN (0): 2635-0823; ISSN (P): 2635-0815

Habitual Miscarriage of Pregnancy with Endocrine Disorders

Mukhammedaminova Diyora Timurovna[1], Nasyrova Khurshidakhon Kudratullayevna[2]

[1]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan. Email: di_khakimova@mail.ru, Orcid ID: 0000-0002-8598-4939

[2]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

Abstract

This article presents information about the relationship of habitual miscarriage with endocrine pathology. Endocrine factors in 75% of cases are the cause of complicated pregnancy up to 20 weeks. Untimely and inadequate therapy of complications of early pregnancy leads to termination of pregnancy not only in the first trimester, but also in later gestation.

Keywords: Habitual Miscarriage, Endocrine Pathology.

Corresponding Author: Mukhammedaminova Diyora Timurovna, Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan.
Email: di_khakimova@mail.ru

Received: 30 April 2022 **Revised: 12 June 2022** **Accepted: 19 June 2022** **Published: 08 July 2022**

Introduction

The relevance of the problem. Habitual miscarriage of pregnancy (PNB) is one of the most difficult medical and social problems, which is addressed by the efforts of leading scientists. According to the WHO definition, PNB is considered to be the presence in the anamnesis of women of three or more spontaneous abortions of pregnancy up to 22 weeks. PNB is a multifactorial, often genetically determined disease; among its causes are endocrine disorders (most often- luteal phase insufficiency and hyperandrogenism), infectious diseases (mainly chronic persistent infections), immune and thrombophilic disorders, malformations of the uterus.[1]

Endocrinological background

In most cases, the reason for termination of pregnancy in the 1st trimester is endocrine pathology, first of all, an incomplete luteal phase that occurs due to hypersecretion of luteinizing hormone (LH), hyposecretion of follicle-stimulating hormone (FSH), hypoestrogenia, hyperandrogenia, endometrial receptor damage.[2]

It is important to note the interdependence of the listed causes of PNB, for example, the level of progesterone has a direct effect on the cytokine system. With a low progesterone content or receptor damage, a low level of progesterone-induced blocking factor was detected. Under these conditions, the mother's immune response to the trophoblast is realized with the pre-possession of type 1 Th, producing mainly pro-inflammatory cytokines TNF-a, IFN-y, IL-1 and IL-6, having a direct embryotoxic effect and contributing to the termination of pregnancy in the 1st trimester. During physiological pregnancy, type 2 cytokines predominate in the blood, including IL-4, blocking cellular immunity reactions and promoting trophoblast invasion.

In this regard, a major role in the genesis of PNB is given to chronic endometritis, which is no less important for implantation and subsequent rejection of the fetal egg than progesterone deficiency. Excessive amount of proinflammatory cytokines leads to activation of prothrombin-zy, which causes thrombosis, trophoblast infarctions and its detachment, and ultimately — termination of pregnancy in the 1st trimester. With continued pregnancy, primary placental insufficiency is formed in the future.

In addition, with the exclusion of all these causes of PNB, idiopathic miscarriages remain (approximately 15%), the pathogenesis of which is unclear.

The epithelium and stroma of the endometrium are rapidly renewing tissues, one of the most sensitive targets of hormonal influences, and under the influence of sex hormones undergo remodeling very quickly. The presence of estrogen receptors in endometrial cells is the leading factor providing the necessary pre-gravidar structural changes. Estrogens provide the processes of endometrial proliferation, while simultaneously inducing the synthesis of progesterone receptors. Insufficient expression of progesterone receptors, as a consequence of inadequate estrogen content, underlies the insufficiency of the luteal phase. However, even with sufficient progesterone production, "morphological immaturity" of the endometrium may be observed. In this regard, not only the level of steroids in the body is important, but also the preservation of all ways of realizing the hormonal effect. At the same time, a series of studies on testing the level of progesterone in PNB showed that the diagnosis of luteal phase insufficiency by the level of progesterone in blood serum is less informative than with morphological examination of the endometrium.

Nevertheless, even if the mechanism of formation of luteal phase insufficiency is not related to the level of progesterone, the mechanism of termination of pregnancy is associated with changes occurring in the endometrium as a result of a violation of secretory transformation caused by insufficient production or inadequate response of the target organ to progesterone. The genesis of this reproductive disorder is due

to the unpreparedness of the endometrium for full-fledged blastocyst invasion and its further development.

In most endometrial biopsies performed during ovular stimulation, there is often a discrepancy between stromal changes and the condition of the glands. The signs of secretory transformation include glandular subnuclear vacuoles, the morphogenesis and role of which remain the subject of discussion.

Given the medical and social significance of the problem of miscarriage, the formation of ways to correct it is a very important task. The introduction of new technologies and treatment methods has led to a decrease in the level of reproductive losses, but has not changed the frequency of the threat of miscarriage, which is still 15-20%. If the therapy of premature birth and late spontaneous miscarriages has been sufficiently studied, then the question of the treatment of miscarriage in the early stages of pregnancy has not found an unambiguous answer. The lack of clear ideas about the mechanism of termination of pregnancy prevents effective pathogenetic therapy.

Stimulation of the endometrial receptor apparatus should be the basis for the preparation of pregnancy in patients with PNB. The modern approach to the treatment of endocrine forms of PNB consists in a combination of hormone therapy with the use of drugs having a direct or indirect effect on the metabolism of steroids. However, the insufficient effectiveness of fertility restoration in endocrine-derived PNB requires the development of new approaches to therapy and improvement of pre-gravidar preparation schemes.

Reproductive losses are the loss of the products of conception at all stages of fetal development as a result of spontaneous or forced termination of pregnancy, stillbirth, as well as the death of children of the first year of life.[3] One of the important components of reproductive losses, especially up to 12 weeks. pregnancy, is an undeveloped pregnancy (NrB). There are no exact statistical data on the frequency of UxO, because in some cases pregnancy ends with spontaneous miscarriage even before the presence or absence of an embryo heartbeat is established. However, even with the difficulties of statistical accounting in the last decade, there has been an increase in both absolute and relative indicators of the frequency of UxO. Thus, out of the number of diagnosed desired pregnancies, one in five ends with spontaneous abortion or UxO in approximately equal proportions, with most of the losses occurring in the early stages of pregnancy.[4] The etiology of UxO is extremely diverse, and a wide diagnostic search is needed to determine the causes of loss in each case. It should be noted that the period during which the examination is carried out (3-6 months) coincides with the period of rehabilitation after termination of pregnancy and pre-pregnancy preparation for the next desired pregnancy. Therefore, the rehabilitation and pre—pregnancy training program should be individual and comprehensive in order to achieve the goal - the birth of a healthy child.

In numerous works, the genesis of NrB is considered from various positions: endocrinological, immunological, genetic, infectious, etc. But, despite a large number of studies devoted to this topic, the final causes of this pathology have not been determined.

If spontaneous termination of pregnancy occurs two or more times in a row, this is already a habitual miscarriage. Its frequency in the population ranges from 2 to 5%.

Miscarriage is a heterogeneous pathology, one of the main places in which endocrine disorders of the reproductive system occupy.

One of the manifestations of disorders of neuroendocrine regulation of a woman's reproductive function is hyperprolactinemia, which occurs in 0.5 - 0.7% of the female population aged 25-40 years. Hyperprolactinemia contributes to insufficient preparation of the endometrium for pregnancy and incomplete implantation of the fetal egg, and can also have its pathological effect on the production of gonadotropins. However, despite the large number of studies devoted to the study of this pathology, many aspects of this problem remain unexplored, in particular, the effect of hyperprolactinemia in women with habitual miscarriage on the course, its outcome for the mother and fetus.

Also, the issue of the influence of individual hormonal disorders on the formation of the symptom complex of a habitual miscarriage is discussed. According to V.P. Kulazhenko, endocrine disorders were observed in 68.5% of women with NrB. Endocrine pathology is observed in 8-20% of cases of habitual pregnancy loss: first of all, it is luteal phase insufficiency (up to 85% of cases), associated with luteinizing hormone hypersecretion, hyperprolactinemia (HyperPRL), hyperandrogenism, thyroid dysfunction, diabetes mellitus, metabolic disorders.

The exact mechanism of the endocrine genesis of pregnancy loss in HyperPRL, which is more common at the age of 25-40 years, has not been fully studied. Hyper PRL contributes to insufficient preparation of the endometrium for pregnancy and incomplete implantation of the fetal egg, has a pathological effect on the production of gonadotropins and the function of the corpus luteum. The role of Hyper PRL in the genesis of female infertility is unambiguous and does not raise questions, in contrast to the information about its effect on NrB, which remains contradictory and insufficient.[5] Special attention should be paid to the fact that the risk of miscarriage in patients with a history of infertility, especially after the use of assisted reproductive technologies, increases significantly. Normalization of prolactin levels in the blood serum, as is known, leads to the restoration of fertility and reduces the risk of termination of pregnancy in the early stages.[6]

The increase in prolactin levels can be caused by a number of hypothalamic-pituitary diseases: hormone-active and inactive formations (prolactin—secreting pituitary adenomas - up to 50% of cases), systemic and vascular pathology, therapeutic measures (radiation therapy, surgery). HyperPRL may be associated with psychopathological states of functional and organic genesis. Mixed, combined forms of Hyper PRL are possible, for example, primary hypothyroidism in combination with prolactinoma.[7]

Dopamine is the main inhibitor of prolactin synthesis and secretion, and it is dopamine agonists that interact with specific D2 receptors on the surface of prolactin-secreting cells that are used to treat Hyper PRL.

Miscarriage - pathophysiological basics

Miscarriage from a pathophysiological standpoint is a universal, integrated response of the female body to any pronounced ill-health of the pregnant woman, fetus, environment and many other factors.

Finding out the causes of habitual miscarriage is extremely important from a practical point of view. Knowing the causes and understanding the pathogenesis of pregnancy termination against the background of hyperprolactinemia, pathogenetic treatment can be carried out more successfully, otherwise it becomes symptomatic and often ineffective.

In connection with the above, it becomes obvious that there is a need for further detailing of existing ideas about the pathogenesis of the development of threatening termination of pregnancy and the development of new principles of therapy, which determined the purpose of our research.

According to the literature, the determination of the level of steroid hormones and chorionic gonadotropin at 9-10 weeks of pregnancy will indicate an already existing pregnancy or predict its unfavorable outcome.[8] Treatment of threatened miscarriage is effective when prescribing therapy up to 7-8 weeks of pregnancy, which allows to prevent its termination with a critical decrease in progesterone levels during luteoplacental shift and to prevent late complications of pregnancy.[9]

Currently, there are no clear criteria in the literature for the comprehensive diagnosis of hormonal disorders and the selection of adequate therapy that allows for the prevention of fetal loss syndrome in women with endocrine forms of miscarriage from the early stages of pregnancy.

Endocrine factors in 75% of cases are the cause of complicated pregnancy up to 20 weeks.[10] According to the literature, untimely and inadequate therapy of complications of early pregnancy leads to termination of pregnancy not only in the first trimester, but also in later gestation.[11,12]

In most cases of threatening termination of pregnancy at an early date, the placentation process is disrupted. Incomplete transformation of spiral arteries and reduced penetration of the trophoblast into the decidual membrane and spiral arteries are especially common, which leads to the development of gestosis, chronic placental insufficiency, premature detachment of the normally located placenta, premature birth.[13] There is a relationship between the severity of arterial hypertension during pregnancy and the degree of placentation disorder.[14]

According to the literature, the determination of the level of steroid hormones and chorionic gonadotropin at 9-10 weeks of pregnancy will indicate an already existing pregnancy or predict its unfavorable outcome.[15] Treatment of threatened miscarriage is effective when prescribing therapy up to 7-8 weeks of pregnancy, which allows to prevent its termination with a critical decrease in progesterone levels during luteoplacental shift and to prevent late complications of pregnancy.[16]

Thus, many authors note that the further course of the gestational process and childbirth in women who have suffered a threatening termination of pregnancy at an early date has significant deviations from the norm. However, it has been noted that the prognosis of pregnancy outcome and, accordingly, perinatal morbidity in these patients largely depends on timely prevention and therapy of placental insufficiency.[17]

Conclusion

Currently, there are no clear criteria in the literature for the comprehensive diagnosis of hormonal disorders and the selection of adequate therapy that allows for the prevention of fetal loss syndrome in women with endocrine forms of miscarriage from the early stages of pregnancy.

References

1. Schindler AE, Carp H, Druckmann R, Genazzani AR, Huber J, Pasqualini J, Schweppe KW, Szekeres-Bartho J. European Progestin Club Guidelines for prevention and treatment of threatened or recurrent (habitual) miscarriage with progestogens. Gynecol Endocrinol. 2015;31(6):447-9. doi: 10.3109/09513590.2015.1017459.
2. Ziganshina MM, Krechetova LV, Vanko LV, Nikolaeva MA, Khodzhaeva ZS, Sukhikh GT. Time course of the cytokine profiles during the early period of normal pregnancy and in patients with a history of habitual miscarriage. Bull Exp Biol Med. 2013;154(3):385-7. doi: 10.1007/s10517-013-1956-0.
3. Bracken MB, Bryce-Buchanan C, Stilten R, Holford T. Menarcheal age and habitual miscarriage: evidence for an association. Ann Hum Biol. 1985;12(6):525-31. doi: 10.1080/03014468500008101.
4. Malyshkina AI, Sotnikova NY, Kroshkina NV, Talanova IE, Kust AV, Kozelkova EV. Peculiarities of the content of peripheral blood cytokines in pregnant women with a habitual miscarriage. Klin Lab Diagn. 2020;65(5):299-303. Russian. doi: 10.18821/0869-2084-2020-65-5-299-303.
5. Mohd Mutalip SS, Ab-Rahim S, Rajikin MH. Vitamin E as an Antioxidant in Female Reproductive Health. Antioxidants (Basel). 2018;7(2):22. doi: 10.3390/antiox7020022.
6. Kaprara A, Krassas GE. Thyroid autoimmunity and miscarriage. Hormones (Athens). 2008;7(4):294-302. doi: 10.14310/horm.2002.1210.
7. Carp HJ, Toder V, Mashiach S, Nebel L, Serr DM. Recurrent miscarriage: a review of current concepts, immune mechanisms, and results of treatment. Obstet Gynecol Surv. 1990;45(10):657-69.
8. Safronova VG, Matveeva NK, Avkhacheva NV, Sidel'nikova VM, Van'ko LV, Sukhikh GT. Changes in regulation of oxidase activity of peripheral blood granulocytes in women with habitual abortions. Bull Exp Biol Med. 2003;136(3):257-60. doi: 10.1023/b:bebm.0000008977.57795.69.
9. Carp H, Torchinsky A, Fein A, Toder V. Hormones, cytokines and fetal anomalies in habitual abortion. Gynecol Endocrinol. 2001;15(6):472-83. doi: 10.1080/gye.15.6.472.483.
10. Dendrinos S, Grigoriou O, Sakkas EG, Makrakis E, Creatsas G. Hysteroscopy in the evaluation of habitual abortions. Eur J Contracept Reprod Health Care. 2008;13(2):198-200. doi: 10.1080/13625180801920032.
11. Dani C, Poggi C. The role of genetic polymorphisms in antioxidant enzymes and potential antioxidant therapies in neonatal lung disease. Antioxid Redox Signal. 2014;21(13):1863-80. doi: 10.1089/ars.2013.5811.
12. Soldo V, Cutura N, Zamurovic M. Threatened miscarriage in the first trimester and retrochorial hematomas: sonographic evaluation and significance. Clin Exp Obstet Gynecol. 2013;40(4):548-50.
13. Wramsby ML, Sten-Linder M, Bremme K. Primary habitual abortions are associated with high frequency of factor V Leiden mutation. Fertil Steril. 2000;74(5):987-91. doi: 10.1016/s0015-0282(00)01545-4.
14. Ilizarova NA, Marinkin IO, Ageeva TA, Bgatova NP, Kuleshov VM, Aidagulova SV. Ultrastructural and histochemical markers of endometrial secretion induction in habitual miscarriage. Bull Exp Biol Med. 2009;148(4):663-7. doi: 10.1007/s10517-010-0790-x.
15. Kaur R, Gupta K. Endocrine dysfunction and recurrent spontaneous abortion: An overview. Int J Appl Basic Med Res. 2016;6(2):79-83. doi:

10.4103/2229-516X.179024.
16. Kolben TM, Rogatsch E, Hester A, Kuhn C, Schmoeckel E, Czogalla B, Mahner S, Jeschke U, Kolben T. Involvement of ILR4α and TLR4 in miscarriages. J Reprod Immunol. 2019;131:36-43. doi: 10.1016/j.jri.2018.12.001.
17. Borzova NY, Ivanenkova NI, Sotnikova NY, Malyshkina AI. [New early prognostic criteria for pregnancy outcome in women with recurrent miscarriage.]. Klin Lab Diagn. 2020;65(5):294-298. Russian. doi: 10.18821/0869-2084-2020-65-5-294-298.

How to cite this article: Timurovna MD, Kudratullayevna NK. Habitual Miscarriage of Pregnancy with Endocrine Disorders. Adv Clin Med Res. 2022;3(3): 5-8.

Source of Support: Nil, **Conflict of Interest:** None declared.