

Causes and Factors of the First Trimester Miscarriage (Literature Review)

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Abstract The aim of the study was to improve the theoretical knowledge of obstetricians-gynecologists, general practitioners, masters and clinical residents about the causes and factors of miscarriage in the first trimester, based on data from foreign and domestic sources. Non-developing pregnancy in the early stages of gestation accounts for up to 20% of pregnancy complications. The main etiologic factors are chromosomal abnormalities, endocrine pathology, immune disorders, genital tract infections, unfavorable lifestyle factors, and male factor. A literature review examines in detail the causes and factors of first trimester miscarriage.

Keywords Miscarriage, Chromosomal abnormalities, Infectious factor, Thrombophilia, Male factor

Over the past decades, impaired reproductive function of couples remains not only a medical but also a socially relevant problem worldwide. Today, the most common complication of pregnancy is miscarriage, with a frequency of 10 to 20% of all clinical pregnancies. The incidence of habitual miscarriage in women of reproductive age is 2–5% and causes various disorders of the reproductive system. Early abortion accounts for 5 to 20% of all pregnancies, and premature birth accounts for 5-10% of all pregnancies [1].

Fetal karyotype abnormalities have a significant importance among the causes of genetic miscarriage, due to the fact that in most cases the chromosomal imbalance of the embryo is the result of a newly arisen mutation in the gamete in one of the parents. Among the significant risk factors of gametogenesis disorders, the age of parents is also important [2-5].

Recently, there has been scientific evidence that the presence of certain gynecological pathology in women, limiting the realization of reproductive function, in particular external endometriosis, is associated with impaired gametogenesis and the formation of aneuploid embryos [6-8]. Due to the rejuvenation of most gynecologic pathologies and their occurrence precisely in the active reproductive age, the above-mentioned data encourage scientists to study miscarriage from the new perspective of genetic studies.

It should be noted that in the case of two or more spontaneous miscarriages the probability of chromosomal aberration (inversion or translocation) in the karyotype of one of the parents increases, and the presence of these structural rearrangements of chromosomes is not accompanied by a change in the number of genes (dose of hereditary material) and, therefore, does not give phenotypic manifestation in

the carrier of this mutation. However, in this case disturbances of meiosis are inevitably developed during the formation of germ cells, which leads to the generation of abnormal gametes and embryos with an unbalanced genome, and consequently to repeated spontaneous abortions of pregnancy.

The aim of the study was to improve the theoretical knowledge of obstetricians-gynecologists, general practitioners, masters and clinical residents about the causes and factors of miscarriage in the first trimester, based on data from foreign and domestic sources.

The main factors leading to pregnancy loss in the first trimester include: embryonic defects - chromosomal abnormalities and teratogenic disorders (rubella, influenza, viral hepatitis, cytomegalovirus, ionizing radiation, various drugs) that interfere with the development of the embryo; maternal factors - endocrine, infectious, anatomical, immunological, genetic changes in the maternal environment; paternal factors, which are determined by the inferiority of spermatogenesis [9].

Embryonic defects (chromosomal abnormalities, teratogenic disorders): One of the main reasons of early miscarriage (EM) is the genetic factor. The antigen system of the human major histocompatibility complex (HLA) provides control, triggering and implementation of the immune response, interaction of all immunocompetent cells of the body, recognition of their own and foreign elements, as well as altered own cells. Polymorphism of major histocompatibility complex genes plays an important role in the normal course of pregnancy. The risk of early fetal loss and infertility may be associated with the presence of certain HLA alleles, as well as spousal concordance on several HLA genes. There is evidence in the literature of a possible correlation between pregnancy failure and autoimmune processes associated with specific HLA alleles [10].

It has been repeatedly pointed out in the scientific medical literature that about 50% of cases of miscarriage are associated with the presence of chromosomal abnormalities (CA) in the embryo/fetus. Traditionally, genomic mutations have been predominantly associated with sporadic miscarriage. Most chromosomal rearrangements in the fetus are thought to be "random" and are not a sign of any maternal disorder [11].

At the same time, it is assumed that, in habitual miscarriage, pathologic changes in the embryo karyotype are much less frequent and make up 3-5% of the cases [12]. It means that in 95-97% of cases of habitual miscarriage, the causes of pregnancy loss can be influenced, provided they are identified in time. However, any logical inferences must be proven by scientific research. Contrary to popular belief, there have been reports in recent years that comparative analysis of the chromosome set in the embryo or fetus in sporadic and habitual miscarriages has not shown a reliable difference in the incidence of chromosomal abnormalities. It is considered to be the most common cause of first trimester miscarriage, regardless of the patient's obstetric history. Some researchers hypothesize that, for some reason, a subset of patients with their own normal karyotype are at increased risk of chromosomal segregation during meiosis or mitosis compared to other age-matched women with similar clinical characteristics. Moreover, in this situation, in each case of an undeveloped pregnancy, completely different chromosomal rearrangements can be found in the products of conception. Unfortunately, the available data to date are insufficient to make a final conclusion about the frequency and structure of CA in the embryo/fetus in sporadic and habitual miscarriage. Therefore, we consider it is necessary to continue the scientific search in this direction, since the obtained data may change the approaches to the examination of patients who have experienced pregnancy loss, as well as improve further pre-conception preparation [13].

However, on the other hand, fetal karyotype anomalies are significant among the causes of miscarriage. In the vast majority of cases, chromosomal imbalance in the embryo is a consequence of a newly occurring mutation in the gamete of one of the parents. One of the most significant risk factors for gametogenesis disorders is the age of parents.

Recently, there is evidence that certain pathology limiting the realization of reproductive function, in particular external endometriosis, is associated with impaired gametogenesis and the formation of aneuploid embryos. In the case of habitual miscarriage (HM) (two or more spontaneous miscarriages), there is an increased probability of the presence of a chromosomal aberration (inversion or translocation) in the karyotype of one of the parents. The presence of these structural rearrangements of chromosomes is not accompanied by a change in the number of genes (dose of hereditary material) and, therefore, does not give a phenotypic manifestation in the carrier of this mutation. However, in this case, a violation of meiosis is inevitably developed during the formation of germ cells, which leads to the formation of abnormal gametes and embryos with an unbalanced genome, and, consequently, to repeated spontaneous abortions [14].

Maternal factors (endocrine, infectious, immunological, genetic changes in the maternal environment). Endocrine factors play a significant role in women with miscarriage. There are numerous confirmations of the connection of embryo death with endocrine disorders among endocrine factors, resulting in luteal phase failure (LPF) and, accordingly, in insufficiently hormone-dependent structural and functional reorganization of the endometrium, which, in turn, does not exclude the occurrence of implantation defects and, in the case of pregnancy, can lead to embryo death in early pregnancy [15].

It is also necessary to note the infectious factor, which is significant in the development of reproductive losses. The presence of an infectious agent in the reproductive organs is one of the leading causes of miscarriage. Chlamydia, Mycoplasma, and *C. albicans* are in the first place in terms of frequency of occurrence. Bacterial infection is one of the main factors influencing the development of late miscarriage, preterm labor and placental insufficiency [16].

However, data of some researchers show that infection is the most significant cause of both sporadic and habitual miscarriage, while other researchers have noted the important role of the infectious factor only for sporadic termination of pregnancy [17].

As it is known, the state of pregnancy is characterized by complex immunological relationships between the body of the mother and the embryo (fetus), which ensure the correct and harmonious development of the fetus, as well as prevent its rejection as a kind of allograft, containing genes foreign to the maternal body of the father of the child [18]. However, at the same time, immune and hormonal changes (shifts) occurring during gestation contribute to increased sensitivity of the maternal organism to infectious agents and increased risk of developing autoimmune processes [19-20].

Maintenance of immunological tolerance towards the embryo (fetus) is ensured by 3 types of immune system cells: regulatory B (Bregs) cells, Regulatory T cells, or Tregs, and dendritic cells (DCs), which closely interact with each other on the principle of feedback through the production of IL-10 and TGF β . Tregs (Th1 and Th2), through the synthesis of proinflammatory (TNF α and IFN- γ) and anti-inflammatory (IL-4, IL-10, IL-13) cytokines, establish maternal-embryonic dialogue, being key regulators of pregnancy. In addition, despite numerous studies in oncology and immunology, the role of Bregs regulatory mechanisms in reproduction remains incompletely understood at present.

Most studies investigating the role of IL-10-producing B cells in the pathogenesis of habitual miscarriage have noted a significant decrease in the levels of CD-19+ cells and IL-10 in the peripheral blood of women with habitual miscarriage (HM) compared to women with normal pregnancy. In addition, many researchers agree that there is a negative correlation between the proportion of IL-10-producing B cells, the total concentration of IgG in plasma and the frequency of abortions, which probably indicates the suppression of autoantibody production by CD-19+ cells and indicates their protective role during gestation [16]. Thus, Bregs contribute significantly

to the development and maintenance of pregnancy by influencing the uterine microenvironment of the embryo through cytokines, as well as inhibiting the aggression of effector cells against semi-allogeneic fetal antigens, making their dysfunction one of the possible key causes of HM progression.

Thrombophilias are inherited and/or acquired conditions that predispose patients to thrombosis. At the level of the reproductive system, they are manifested by a number of reproductive failures, primarily by habitual miscarriage. Among the most frequent causes of reproductively significant thrombophilias are hereditary thrombophilias (primarily mutations in the F2 and F5 genes), hyperhomocysteinemia, protein S and C deficiency and antiphospholipid syndrome. The fundamental pathogenetic mechanism of antiphospholipid syndrome (APS) is the activation of cellular immunity and the synthesis of antiphospholipid antibodies (APL): anticardiolipin antibodies (AKA), and/or lupus anticoagulant (LA), and/or antibodies to β 2-glycoprotein -I (anti- β 2GPI). At the level of the vascular system of the uteroplacental complex, APS is realized in the form of thrombosis, which leads to placental disorders, manifested by fetal growth retardation syndrome, fetal hypoxia up to its death, and early manifestation of symptoms of preeclampsia. Антифосфолипидный синдром влечет за собой череду репродуктивных потерь и, как следствие, обилие внутриматочных вмешательств. Trauma to the basal layer of the endometrium that occurs during such manipulations is a predisposing factor for the development of Asherman's syndrome with the formation of intrauterine adhesions (IUD) and is manifested by hypo- or amenorrhea (62%), infertility and miscarriage (43%) [21].

Paternal factors. As a separate factor in the development of pathological pregnancy, the so-called male factor is distinguished - a disorder that occurs during spermatogenesis [22]. A meta-analysis of data from 16 large-scale studies showed that high levels of paternal sperm DNA fragmentation significantly increased the risk of spontaneous miscarriage. It is currently known that many components of seminal plasma (glycodelin, salivary-sperm globulin, beta-globulin) create conditions necessary for the normal functioning and viability of spermium and the formation of a full-fledged fertilized egg and the disruption of their parameters, and can also be considered as one of the causes of miscarriage.

Among the possible causes of habitual miscarriage, tobacco smoking, alcohol abuse, drug addiction, metabolic and endocrine disorders, immune and infectious factors are considered important. According to J.A. Alegria-Torres et al. and R.N. Dashwood et al. hypodynamia combined with obesity can lead to histone modification and microRNA expression and as a consequence is a risk factor for spontaneous miscarriage [23]. Older reproductive age and genetic abnormalities are the leading causes of spontaneous miscarriage [24].

Conclusion

Thus, the variety of risk factors and causes of anembryonic pregnancy increase the risk of subsequent anembryonic

pregnancy.

Therefore, every woman with a history of at least one anembryonic pregnancy should be fully examined, all possible causes should be found and eliminated, and pregravidarial preparation for the next pregnancy should be started.

Conflict of interests

The authors declare no conflict of interest.

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REFERENCES

- [1] The issue of pregravidar preparation of women with habitual miscarriage / G. V. Bylym, O. V. Noskova, E. V. Litvinova [et al] // Bulletin of Hygiene and Epidemiology. \ \ In Russian. \ \ 2022; 26(3). – p. 237-241. – EDN TUOLJC.
- [2] Preimplantation genetic diagnostics of embryos in the IVF program as a way of profiling hereditary pathology / I. Fetisova (et al) // Bulletin of Ivanovo Medical Academy. \ \ In Russian. \ \ 2018; 23(3) -p. 10-13.
- [3] Results of preimplantation genetic testing of embryos in patients of late reproductive age / I.N. Fetisova (et al.) // Bulletin of Ivanovo Medical Academy. \ \ In Russian. \ \ 2019; 24(2). -p. 36-38.
- [4] Farg D. and Hassan H. Obstetric Outcomes for Teenage and Adult Pregnancy: A Comparative Study. Nursing & Care Open Access Journal, 2020; 7(1): 1-10. doi:10.15406/ncoaj.2020.07.00208.
- [5] Malk R., Hassan E., Mohamed A., Amr E., Hassan H. Effect of an Educational Program on Nurses Performance Regarding COVID-19 in the Obstetrics and Surgical units. Egyptian Journal of Health Care, 2022; 13(4): 251-269. DOI: 10.21608/EJHC.2022.260885.
- [6] Fetisov N.S. Preimplantation genetic testing in endometriosis-associated infertility / N.S. Fetisova, I.N. Fetisova // "Medico-biological, clinical and social issues of human health and pathology": XV regional festival "Young scientists-development of Ivanovo region": V All-Russian Scientific Conf. of Students and Young Scientists with International Participation. \ \ In Russian. \ \ - 2019. - p.3-6.
- [7] Hassan H. The Impact of Evidence-Based Nursing as The Foundation for Professional Maternity Nursing Practices. Open Access Journal of Reproductive System and Sexual Disorder, 2019; 2(2): 195-197. OAJRSD.MS.ID.000135. DOI: 10.32474/OAJRSD.2019.02.000135.
- [8] Hassan H. Evidence-Based Practice in Midwifery and Maternity Nursing for Excellent Quality of Care Outcomes. American Journal of Nursing Research, 2020; 8(6): 606-607. doi: 10.12691/ajnr-8-6-3.
- [9] Lanshchakova P.E. New approaches to diagnosis, treatment and rehabilitation of women with undeveloped pregnancy. Dissertation for the degree of Candidate of Medical Sciences. \ \ In Russian. \ \ 2019.

- [10] The relationship of HLA-genes with habitual miscarriage. / A.N. Kiseleva, E.V. Butina, N.V. Isaeva, E.A. Poponina // Hematology Bulletin. \ In Russian. \ 2021; 17(3). – p. 49. – EDN TPBCNQ.
- [11] Kudryavtseva E.V., Kovalev V.V., Kanivets I.V., Kievskaya Y.K., Korostelev S.A. Fetal Free-DNA: experience of population screening of chromosomal pathology in Russia. Issues of gynecology, obstetrics and perinatology. \ In Russian. \ 2019; 18(3): 46-51. DOI: 10.20953/1726-1678-2019-3-46-51.
- [12] Structure of the causes of miscarriage in women with habitual miscarriage / E. N. Grudnitskaya, S. L. Voskresensky, L. M. Nebyshynets [et al] // Modern perinatal medical technologies in solving problems of demographic security. \ In Russian. \ 2022. – № 15. – p. 63-68. – EDN GZRVLN.
- [13] The role of chromosomal aberrations of the embryo in the genesis of habitual and sporadic miscarriage. / E. V. Kudryavtseva, V. V. Kovalev, I. I. Baranov [et al] // Issues of gynecology, obstetrics and perinatology. \ In Russian. \ 2021; 20(1). – p. 34-39. – DOI 10.20953/1726-1678-2021-1-34-39. – EDN PWZWDM.
- [14] Chromosomal aberrations as a cause of habitual miscarriage of pregnancy / I. N. Fetisova, A. I. Malyshkina, S. Y. Ratnikova [et al] // Bulletin of the Ivanovo Medical Academy. \ In Russian. \ 2019; 24(4). – p. 39-43. – EDN UZTOSJ.
- [15] Predictors of undeveloped pregnancy and the role of pregravidar preparation in the prevention of repeated reproductive losses / Z. S. Romyantseva, E. Yu. Lyumanova, N. I. Volotskaya, S. S. Anikin // Vyatka Medical Bulletin. \ In Russian. \ 2021; 1(69). – p. 64-69. – DOI 10.24411/2220-7880-2021-10154. – EDN HFFWGK.
- [16] Abdullaeva, Z. G. Role of infectious agent in habitual and spontaneous miscarriage of pregnancy / Z. G. Abdullaeva, A. A. Zimina, A. V. Smirnova // Medico-biological, clinical and social issues of human health and pathology: Materials of the X All-Russian scientific conference of students and young scientists with international participation, held as part of the "Decade of Science and Technology" \ In Russian. \ Ivanovo, April 02, 2024. - Ivanovo: Ivanovo State Medical University, 2024. - p. 220-222. – EDN JTKTRB.
- [17] Infectious status in women with a history of threatened abortion and habitual miscarriage / A. V. Kust, E. V. Kozelkova, A. V. Sadygova [et al] // Russian Journal of Immunology. \ In Russian. \ 2019; 13(20-1(22)). – p. 362-364. – DOI 10.31857/S102872210006628-5. – EDN CHLRGI.
- [18] Kolte A. M. Chance of live birth: a nationwide, registry-based cohort study / A. M. Kolte, D. Westergaard et al. // Human reproduction. - England: Oxford, 2021. - № 36(4). - P. 1065–1073. DOI: 10.1093/humrep/deaa326.
- [19] Dijk V. Recurrent pregnancy loss: diagnostic workup after two or three pregnancy losses? A systematic review of the literature and meta-analysis / V. Dijk, A. M. Kolte et al. // Human reproduction update. - 2020. - № 26(3). - P. 356–367. DOI: 10.1093/humupd/dmz048.
- [20] Habitual miscarriage of pregnancy / N. S. Dronova, D. A. Yakovenko, R. Sh. Sarkisyan [et al] // International Research Journal. \ In Russian. \ 2024; 5(143). – DOI 10.60797/IRJ. 2024.143.34. – EDN MIUZYNY.
- [21] A case of successful completion of pregnancy in a patient with a history of habitual miscarriage against the background of combined thrombophilia / A. G. Yashchuk, I. B. Fatkullina, A. V. Maslennikov [et al] // Medical Alphabet. \ In Russian. \ 2019; 4(33) (408). – p. 54-56. – DOI 10.33667/2078-5631-2019-4-33(408)-54-56. – EDN NJGLPY.
- [22] Puschek E., Scott Lucidi R. FACOG Early Pregnancy loss . Practise essencial. Updated: Jun 08, 2018.
- [23] Male factor of infertility in the aspect of miscarriage / M. N. Korshunov, E. S. Korshunova, Y. V. Kastrikin, S. P. Darenkov // Kremlin Medicine. Clinical Bulletin. \ In Russian. \ 2021; 3. p. 78-82. – DOI 10.26269/n3bk-c996. – EDN QXJTIQ.
- [24] Li YH, Marren A. Recurrent pregnancy loss. Australian journal of general practice. //Aust J Gen Pract. – 2018. – V. 47. №.7. – P. 432-436. doi: 10.31128/AJGP-01-18-4459.