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EPIDEMIOLOGICAL ASPECTS OF PREGNANT LOSSES. LITERATURE REVIEW.

Ayaulym N. Blushinova¹, <https://orcid.org/0000-0003-3939-3860>

Gulnara M. Shalgumbayeva¹ <http://orcid.org/0000-0003-3310-4490>

Duman Berikuly¹, <https://orcid.org/0000-0002-9738-7453>

Zaituna G. Khamidullina², <https://orcid.org/0000-0002-5324-8486>

Gaukhar A. Korganbayeva¹, <https://orcid.org/0000-0001-5257-1495>

Inabat N. Ordabayeva¹, <https://orcid.org/0000-0003-0209-0962>

Nazerke K. Sailauova¹, <https://orcid.org/0000-0003-3443-8847>

Aiym B. Bekezhan¹, <https://orcid.org/0000-0002-0140-4897>

¹ NCJSC “Semey medical university”, Semey, Republic of Kazakhstan;

² NCJSC «Astana medical university», Astana c., Republic of Kazakhstan.

Abstract

Relevance. Miscarriage is a spontaneous termination of pregnancy that leads to death at any time from implantation to delivery. Miscarriage affects about a third of pregnancies and most often occurs before the onset of viability during the first and beginning of the second trimesters. This is often an unfavorable event for both women and their partners and can be associated with significant psychological trauma. Despite the frequency and potentially alarming nature of miscarriage, its pathophysiology remains poorly understood, and its history, including the temporal ordering of signs and symptoms, in the early stages of pregnancy has not yet been fully described. In this literature review, we will try to describe the causes and frequency of the spread of early and recurrent miscarriage.

Objective. To analyze the literature data on the causes and frequency of prevalence of early and recurrent miscarriage.

Search strategy. The study examined full-text publications in English, which are devoted to early and recurrent miscarriage of pregnancy. In the process of literature review, the following search engines were used: Pubmed, Web of science, Scopus, Google Scholar by keywords. The time period was designated 2012-2022. *The criteria for inclusion of publications in the review* were as follows: full-text publications in English, which are publicly available and contain statistically confirmed conclusions. *Exclusion criteria:* summary reports, newspaper articles and personal messages. 230 publications have been identified on this topic. Of these, 68 publications corresponded to the purpose of our study.

Results and conclusions. Human reproductive health still faces serious problems. More and more couples are struggling with conception. However, the biggest problem is still the high frequency of pregnancy loss after successful conception. Previous studies have documented about 10% of registered pregnancy losses, however, another 10-15% of early losses have never been observed in a hospital or clinic and, therefore, were not registered in the registers of diagnoses at discharge. Some of these losses occur so early in pregnancy that women do not perceive them as pregnancy loss.

Key words: miscarriage, early pregnancy loss, recurrent pregnancy loss.

Резюме

ЭПИДЕМИОЛОГИЧЕСКИЕ АСПЕКТЫ НЕВЫНАШИВАНИЯ БЕРЕМЕННОСТИ. ОБЗОР ЛИТЕРАТУРЫ.

Аяулым Н. Блушинова¹, <https://orcid.org/0000-0003-3939-3860>

Гулнара М. Шалгумбаева¹, <http://orcid.org/0000-0003-3310-4490>

Думан Берікұлы¹, <https://orcid.org/0000-0002-9738-7453>

Зайтуна Г. Хамидуллинка², <https://orcid.org/0000-0002-5324-8486>

Гаухар А. Корганбаева¹, <https://orcid.org/0000-0001-5257-1495>

Инабат Н. Ордабаева¹, <https://orcid.org/0000-0003-0209-0962>

Назерке Қ. Сайлауова¹, <https://orcid.org/0000-0003-3443-8847>

Айым Б. Бекежан¹, <https://orcid.org/0000-0002-0140-4897>

¹ НАО «Медицинский университет Семей», г. Семей, Республика Казахстан;

² НАО «Медицинский университет Астана», г. Астана, Республика Казахстан.

Актуальность. Невынашивание беременности - это самопроизвольное прерывание беременности, приводящее к смерти в любой момент от имплантации до родов. Невынашивание беременности затрагивает примерно треть беременностей и чаще всего происходит до наступления жизнеспособности в течение первого и начала второго

триместров. Это часто неблагоприятное событие как для женщин, так и для их партнеров и может быть связано со значительной психологической травмой. Несмотря на частоту и потенциально тревожный характер невынашивания беременности, ее патофизиология остается малоизученной, и ее история, включая временную упорядоченность признаков и симптомов, на ранних сроках беременности еще не полностью описана. В данном обзоре литературы мы попытаемся описать причины и частоту распространения раннего и повторного невынашивания беременности.

Цель. Провести анализ данных литературы по причинам и частоте распространенности раннего и повторного невынашивания беременности.

Стратегия поиска. В исследовании изучены полнотекстовые публикации на английском языке, которые посвящены раннему и повторному невынашиванию беременности. В процессе поиска литературы использованы следующие поисковые системы: Pubmed, Web of science, Scopus, Google Scholar по ключевым словам. Временной период был обозначен 2012-2022 годами. *Критерии включения публикаций в обзор были следующими:* полнотекстовые публикации на английском языке, находящиеся в открытом доступе и содержащие статистически подтвержденные выводы. *Критерии исключения:* краткие отчеты, газетные статьи и личные сообщения. По данной теме выявлено 230 публикаций. Из них цели нашего исследования соответствовало 68 публикаций.

Результаты и выводы. Репродуктивное здоровье человека по-прежнему сталкивается с серьезными проблемами. Всебольше пар борются с зачатием. Однако самой большой проблемой по-прежнему остается высокая частота потери беременности после успешного зачатия. Предыдущие исследования задокументировали порядка 10% зарегистрированных потерь беременности, однако, еще 10-15% ранних потерь никогда не наблюдались в больнице или клинике и, следовательно, не регистрировались в регистрах диагнозов при выписке. Некоторые из этих потерь происходят на столь ранних сроках беременности, что женщины не воспринимают их как потерю беременности.

Ключевые слова: невынашивание беременности, выкидыш, ранняя потеря беременности.

Түйіндеме

ЖҮКТІЛІКТІҢ ҮЗІЛУІНІҢ ЭПИДЕМИОЛОГИЯЛЫҚ АСПЕКТІЛЕРІ. ӘДЕБИЕТТІК ШОЛУ.

Аялым Н. Блушінова¹, <https://orcid.org/0000-0003-3939-3860>

Гульнара М. Шалгумбаева¹, <http://orcid.org/0000-0003-3310-4490>

Думан Берікұлы¹, <https://orcid.org/0000-0002-9738-7453>

Зайтуна Г. Хамидуллина², <https://orcid.org/0000-0002-5324-8486>

Гаухар А. Корганбаева¹, <https://orcid.org/0000-0001-5257-1495>

Инабат Н. Ордабаева¹, <https://orcid.org/0000-0003-0209-0962>

Назерке Қ. Сайлауова¹, <https://orcid.org/0000-0003-3443-8847>

Айым Б. Бекежан¹, <https://orcid.org/0000-0002-0140-4897>

¹ КеАҚ «Семей медицина университеті», Семей қ., Қазақстан Республикасы;

² КеАҚ "Астана медицина университеті", Астана қ., Қазақстан Республикасы.

Түйін. Жүктіліктің үзілуі - бұл жүктіліктің өздігінен тоқтатылуы, имплантациядан босануға дейін кез-келген уақытта өлімге әкеледі. Жүктіліктің үзілуі жүктіліктің үштен біріне әсер етеді және көбінесе бірінші және екінші триместрдің басында өміршеңдік басталғанға дейін болады. Бұл көбінесе әйелдер үшін де, олардың серіктестері үшін де қолайсыз оқиға және айтарлықтай психологиялық жарақатпен байланысты болуы мүмкін. Жүктіліктің жиі және ықтимал алаңдаушылық сипатына қарамастан, оның патофизиологиясы нашар түсініледі және оның тарихы, оның ішінде белгілердің уақытша реттілігі әлі толық сипатталмаған. Әдебиеттерге осы шолуда біз жүктіліктің ерте және қайталама таралуының себептері мен жиілігін сипаттауға тырысамыз.

Мақсаты. Жүктіліктің үзілуінің ерте және қайта түрлерінің себептері мен жиілігі туралы әдебиеттерге талдау жүргізу.

Іздеу стратегиясы. Зерттеу ерте және қайталама жүктіліктің үзілуіне арналған ағылшын тіліндегі толық мәтінді басылымдарды зерттеді. Әдебиеттерді іздеу барысында келесі іздеу жүйелері қолданылды: Pubmed, Web of science, Scopus, Google Scholar. Уақыт кезеңі 2012-2022 жылдармен белгіленді. *Жарияланымдарды шолуға қосу критерийлері мыналар болды:* ашық қолжетімділіктегі және статистикалық расталған қорытындылары бар ағылшын тіліндегі толық мәтінді жарияланымдар. *Ерекшелік критерийлері:* қысқаша есептер, газет мақалалары және жеке хабарламалар. Осы тақырып бойынша 230 жарияланым анықталды. Олардың ішінде біздің зерттеуіміздің мақсатына 68 басылым сәйкес келді.

Нәтижелер мен қорытындылар. Адамның репродуктивті денсаулығы әлі де күрделі проблемаларға тап болуда. Алайда, сәтті жүкті болудан кейін жүктіліктің үзілуінің жоғары деңгейі әлі де үлкен проблема болып табылады. Алдыңғы зерттеулер жүктіліктің тіркелген шығындарының шамамен 10% - ын құжаттады, алайда ерте шығындардың тағы 10-15% - ы ауруханада немесе клиникада ешқашан байқалмады, сондықтан шығарылған кезде диагноз регистрлерінде тіркелмеген. Бұл шығындардың кейбіреулері жүктіліктің ерте кезеңдерінде пайда болады, сондықтан әйелдер оларды жүктіліктің үзілуі ретінде қабылдамайды.

Түйінді сөздер: жүктілік, түсік түсіру, жүктіліктің ерте үзілуі.

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Introduction

Miscarriage is a spontaneous termination of pregnancy that leads to death at any time from implantation to delivery. According to a systematic review of Supra K. early miscarriage affects about one third of pregnancies and most often occurs before the onset of viability during the first and beginning of the second trimesters. This is often an unfavorable event for both women and their partners and can be associated with significant psychological trauma. Despite the frequency and potentially alarming nature of miscarriage, its pathophysiology remains poorly understood, and its history, including the temporal ordering of signs and symptoms, in the early stages of pregnancy has not yet been fully described. In this literature review, we will try to describe the causes and frequency of the spread of early and repeated miscarriage[56].

Objective. To analyze the literature data on the causes and frequency of prevalence of early and recurrent miscarriage.

Search strategy. The study examined full-text publications in English, which are devoted to early and recurrent miscarriage of pregnancy. In the process of literature review, the following search engines were used: Pubmed, Web of science, Scopus, Google Scholar by keywords. The time period was designated 2012-2022. The criteria for inclusion of publications in the review were as follows: full-text publications in English, which are publicly available and contain statistically confirmed conclusions. Exclusion criteria: summary reports, newspaper articles and personal messages. 230 publications have been identified on this topic. Of these, 68 publications corresponded to the purpose of our study.

Early pregnancy loss

Early pregnancy loss - this is an intrauterine pregnancy, diagnosed before 12 weeks, 6 days of pregnancy[68]. The probability of an EPL prognosis is impossible, since a miscarriage may occur before the patient finds out that she is pregnant. In a 1988 study, the incidence of EPL was estimated at 31%[25] and included clinically recognized and unrecognized pregnancies (detected before clinical diagnosis). More recent publications report cases of 12.8% to 13.5%; however, they are based only on clinically confirmed pregnancies [37, 55]. In the presence of highly sensitive over-the-counter pregnancy urine tests, which can detect pregnancy before an official clinical diagnosis, the frequency of EPL is probably higher than that published for clinically confirmed pregnancies. Because EPL is a common disease, doctors should be familiar with its terminology, risk factors for the mother, manifestations, diagnosis and treatment.

Causes of early miscarriage

The most common cause of miscarriage is a chromosomal abnormality, such as aneuploidy or triploidy, which is incompatible with life. Although this etiology is very common, it

is important to recognize other causes that lead to EPL. Cases of women with recurrent miscarriage, in whom the frequency of euploid miscarriages is higher, were considered. In fact, the normal karyotype of an embryo or fetus may to some extent predict subsequent miscarriage in this population, since it indicates a different, more likely ongoing etiology [47].

According to the literature data, the causes of miscarriage in early pregnancy can be generally divided into six categories:

1. genetic causes
2. infectious causes
3. immunological causes
4. implantation anomalies
5. anatomical abnormalities of the uterus
6. endocrine disorders

Genetic causes

A chromosomal defect is the cause of 50% to 60% of early spontaneous miscarriages. Chromosomal abnormalities are more common in earlier pregnancy, while cytogenetic abnormalities are detected in 70% of cases before 6 weeks of pregnancy [19]. Cytogenetic anomalies can be detected using a conventional karyotype, a chromosomal microchip, amplification of a probe dependent on multiplex ligation, and quantitative fluorescent polymerase chain reaction. In general, karyotypic testing is carried out with varying success, ranging from 49% to 93%, depending on the interval from death to cultivation and on the collection technique. The chromosome microchip is largely practical and useful. Samples for a chromosomal microchip are successfully collected in 99% of cases, and a microchip with a single nucleotide polymorphism detects 13% of anomalies that were absent with a standard karyotype [36]. However, the cost of this test remains prohibitively high in many conditions, and the Committee of the American College of Obstetricians and Gynecologists currently does not recommend the routine use of single-nucleotide polymorphism of microchips to evaluate the products of conception.

Infectious causes

According to some researchers, there are too many infectious agents involved in sporadic miscarriage to list them in full. In fact, any systemic infection in the mother can lead to miscarriage either as a result of hematogenous transmission to the fetal placental region, or as a result of sepsis in the mother and hemodynamic disorders [59]. Many microorganisms have the ability to transplacental infection, although some of them are less associated with miscarriage in the early stages than others [1].

Viral infections such as cytomegalovirus, herpes simplex virus type 1 and 2, human parvovirus B19, enterovirus, adenovirus and chickenpox virus have been implicated as causative agents of spontaneous abortions[1], although a more

recent study using real-time qPCR did not show that they are as significant a cause as originally assumed [65]. Viral infections may be associated with certain pathognomonic histological diagnostic signs, such as inclusions found in cytomegalovirus, adenovirus or herpes simplex. In addition, *Treponema pallidum* (syphilis), *Toxoplasma gondii* (toxoplasmosis), *Listeria monocytogenes* and *Plasmodium falciparum* (malaria) are all capable of causing transplacental infection. Bacterial infections usually cause acute deciduitis, which is associated with premature pregnancy loss. These pathological samples may contain fragments of tissue with abundant exudate, but the results are non-specific.

Anomalies with a probable immunological basis

Massive deposition of fibrin in the interstices (also called uterine fundus infarction in placental pathology) is a process that not only leads to loss in the first trimester of pregnancy, but also has a significant potential for relapse in subsequent pregnancies. This disease is manifested by large accumulations of fibrin that surround the chorionic villi along the basal and chorionic plates in response to damage [58]. Various disorders can lead to damage to the villous interface between mother and fetus, including maternal thrombophilia, which leads to increased deposition of fibrin or violation of the integrity of the villous trophoblast, which leads to the effect of tissue factor and activates the cascade of blood clotting locally on the surface of the villi. This damage to syncytiotrophoblasts can be caused by external factors, such as maternal antiphospholipid antibodies, or internal factors, such as deficiency of long-chain fatty acids in the fetus [48].

Chronic villitis, histological chronic inflammation of the villous parenchyma, is observed in placentas of the first trimester of pregnancy. In the largest number of cases, the infectious etiology was not established, which led to the fact that the inflammation was called willitis of unknown etiology. These cases are mainly considered as arising from aberrant maternal cell-mediated immune responses to fetal antigens. In some patients, disease progression and subsequent repeated pregnancy loss are observed [28].

Chronic intervillitis is a separate disease, the pathological sign of which is the presence of dense clusters of histiocytes in the space of maternal blood between the villi, with the presence or absence of perivillous fibrin deposition. It is present in less than 1% of miscarriages in the first trimester of pregnancy. Patients with chronic intervillitis, the etiology of which is unknown, have recurrent early miscarriages, as well as pregnancies with complications caused by severe growth restrictions or stillbirth [48].

Anomalies during implantation

Implantation of a blastocyst is a very complex process involving many cellular and tissue components; thus, the probability of miscarriage due to one abnormal factor at this stage of development is very high. For successful implantation, many factors must function optimally, including the correct maturation of the surface epithelium, the correct amount and composition of endometrial secretions, the correct number and types of immunocompetent maternal cells that interact with the trophoblast on the blastocyst, and the correct receptors for the invading trophoblast so that their invasive progress through the maternal tissue is not stopped or blunted [67]. Currently, there is no data on the exact distribution and frequency of all disorders that may jeopardize implantation. In approximately two-thirds of cases of unsuccessful pregnancy in the early

stages, anatomical signs of defective placentation are found, which is mainly characterized by a thinner and fragmented trophoblast shell and reduced extravillary invasion of the cytotrophoblast into the lumen at the ends of spiral arteries [56]. In most cases, this is due to the premature onset of maternal arterial circulation throughout the placenta. Since maternal arterial pO₂ is hyperoxic to the newly implanted embryo, this premature perfusion leads to widespread oxidative damage to trophoblasts and placental degeneration. In these cases, maternal arteries located near the implantation site, which do not show typical and necessary changes in trophoblastic conversion, can be pathologically identified [25].

Anatomical abnormalities of the uterus

In the general population, the incidence of uterine malformations is 9.8%, with the most common being arcuate and partial septum abnormalities. Up to 13-19% of women with recurrent spontaneous miscarriages have a malformation of the uterus [26]. Septate and partially septate uterus are associated with an increase in the frequency of miscarriages in the first trimester in a systematic review (OR 2.89; 95% CI 1.024–0.14) [35]. Some observational data suggest that metroplasty may improve obstetric outcomes in women with uterine septa, but this has not yet been confirmed by randomized trials. In addition, many women with these abnormalities have normal obstetric outcomes [26].

Endocrine factors

There is evidence that thyroid dysfunction and thyroid autoimmunity are associated with infertility and pregnancy loss both in a situation where a woman has an euthyroid system with antibodies to the thyroid gland, and in a woman with a negative level of antibodies to the thyroid gland with an increased level of thyroid-stimulating hormone [61].

Patient management

The management of a patient with EPL depends on its form and diagnosis. If the patient has a hemodynamically stable condition, pregnancy less than 13 weeks 6 days and fever, it is necessary to consider the possibility of waiting management with training the patient to monitor for excessive bleeding or signs of infection. A complete abortion in a Rhesus-positive patient does not require medical or surgical treatment, but the patient should be properly informed about the expectations of a future pregnancy. If another pregnancy is desired, sexual rest is required, recommended within 2 weeks after the disappearance of symptoms, after which the patient can resume further attempts at conception [67]. It is necessary to consult on contraception if a subsequent pregnancy is undesirable. Patients with Rh-negative conflict should receive Rho (D) immunoglobulin. In patients with incomplete abortion who are in a state of afebrility and hemodynamically stable, one dose of mifepristone 200 mg orally (if available) can be used 24 hours before a single administration of misoprostol 800 mcg vaginally. If mifepristone is not available, only misoprostol can still be used. If the products of conception still persist after 1 week, and if the patient has a hemodynamically stable and afebrile temperature, consider a second dose of misoprostol. Bleeding can be stopped with methylergonovine at a dose of 0.2 mg orally every 6-8 hours, but the patient should be advised to immediately report a worsening of symptoms [25]. Surgical intervention is required if the patient has a pregnancy of more than 13 weeks, hemodynamically unstable, septic, severe bleeding and if the products of conception remain intact [4, 52]. Follow-up of a patient who has undergone EPL includes

sequential administration of beta-hCG. The diagnosis of EPL can be devastating for patients and their partners and is often associated with other physical and psychological diagnoses. Feelings of guilt, shame, and isolation are common and can lead to diagnoses of depression and anxiety. A history of EPL can also have long-term consequences for the mother's health. Recent studies have shown an increased incidence of type 2 diabetes, hypercholesterolemia and hypertension in women [25].

Recurrent pregnancy loss

Recurrent pregnancy loss a severe pregnancy disorder experienced by ~2.5% of women trying to get pregnant [17]. Habitual miscarriage is defined as the failure of two or more clinically confirmed pregnancies before 20-24 weeks and includes the loss of the embryo and fetus [17]. Diagnosis of miscarriages in the early stages is relatively simple, although progress in predicting and preventing repeated pregnancy loss is hampered by the lack of standardized definitions, uncertainty associated with pathogenesis, and high variability of the clinical picture. The prognosis for couples with repeated pregnancy loss is usually good, although the probability of a successful pregnancy depends on the age of the mother and the number of previous losses. Recurrent pregnancy loss can be caused by chromosomal abnormalities, anatomical defects of the uterus, autoimmune disorders and endometrial dysfunction [23]. The available treatments target the perceived risk factors for pregnancy loss, although the effectiveness of many medical interventions is controversial. Regardless of the underlying etiology, married couples need to be provided with accurate information about their chances of having a child and appropriate support to reduce the psychological burden associated with multiple miscarriages [23]. Future studies should examine the pathogenesis of repeated pregnancy loss and evaluate new diagnostic tests and treatment methods in adequate clinical trials.

Causes and risk factors

Genetic factors

Embryonic aneuploidy

Embryonic aneuploidy is a common cause of recurrent pregnancy losses [11, 39, 46, 64]. Based on traditional genetic analyses such as karyotyping, the frequency of chromosomal abnormalities appears to be lower in women with repeated pregnancy loss than in women with spontaneous pregnancy loss [54]. However, more sensitive analyses, including next-generation sequencing and chromosome arrays, have shown that the frequency of embryonic aneuploidy may be equivalent with repeated and spontaneous pregnancy loss. [20, 22, 49, 51, 57, 62]. It should be noted that care must be taken when interpreting the results of any analysis. Genetic mosaicism can exist in blastomeres and trophoblast cells in embryos, and compensatory mechanisms that either eliminate aneuploid cells or restrict these cells to placental cell lines can lead to a successful pregnancy [60]. Indeed, analysis of chorionic villi samples showed that 1% of ongoing pregnancies have limited placental trisomy at 11-14 weeks gestation [17].

Parental chromosomal structural abnormalities

Parental translocations, inversions, and copy number variations are more common in couples with repeated pregnancy loss (2-5%) than in the general population (0.7%) [19, 47]. The differences in reported prevalence between studies probably reflect the sensitivity of different diagnostic methods; for example, the rates are lower in studies that used Gimse banding than in studies that used next-generation

sequencing [60]. As mentioned earlier, a genome-wide association study revealed four different susceptibility loci associated with progesterone production, placentation, and gonadotropin regulation, which are associated with sporadic and recurrent pregnancy loss [33].

Defective sperm.

The question of whether abnormalities in sperm contribute to repeated pregnancy loss is being discussed. Some studies have found epigenetic modifications of sperm DNA [24] and increased DNA fragmentation in spermatozoa, which may contribute to repeated pregnancy loss [10, 66]. However, a large study involving women who underwent in vitro fertilization (IVF), who required intracytoplasmic sperm injection, did not find a clear link between the level of sperm DNA fragmentation and the risk of miscarriage [30]. In addition, aneuploidies are found in 1-5% of spermatozoa, but there is no noticeable age association [40].

Uterine factors

Anatomical factors

Structural abnormalities of the uterus are often diagnosed during fertility studies. Congenital anomalies of the uterus, including arched, septate, one-horned, two-horned and didelphic uterus, are more common in women who have suffered pregnancy loss (13.3%, 95% CI 8.9-20.0%) than in the general population (5.5%, 95% CI 3.5-8.5%). In addition, the prevalence of congenital malformations of the uterus, especially the uterine septum, is lower in women with secondary recurrent pregnancy loss (4.6%) than in women with primary recurrent pregnancy loss (9.0%) [27]. Congenital anomalies are more often associated with miscarriages in the late stages of the first and second trimesters, rather than with miscarriages in the early stages, although the exact mechanisms by which a congenital anomaly causes pregnancy failure remain controversial [17].

Chronic endometritis

Chronic endometritis is often asymptomatic or accompanied by mild nonspecific symptoms [50], which makes it difficult to assess its prevalence in the general population. The registered prevalence in women with repeated pregnancy loss ranges from 9% to 56% [8, 14, 41]; such a wide variation in estimates is probably due to the lack of agreed diagnostic criteria (the range of plasma cells required for a positive diagnosis). It has been suggested that chronic endometritis causes pregnancy loss by promoting the penetration of immune cells into the endometrium [53]. However, there are several studies demonstrating altered infiltration of immune cells other than plasma cells, and there is no experimental evidence confirming that altered infiltration of endometrial immune cells in chronic endometritis is the cause of recurrent pregnancy loss [17]. Limited data from observational studies indicate improved outcomes in women with recurrent pregnancy loss who have chronic endometritis after antibiotic treatment; however, the effectiveness of antibiotic treatment has not yet been evaluated in randomized controlled trials [23].

Luteal phase defect

Due to the critical role of sustained progesterone signaling for implantation and pregnancy, low progesterone production during the luteal phase of the menstrual cycle is widely regarded as an important cause of miscarriage. However, attempts to identify luteal phase defects in women with recurrent pregnancy loss were unsuccessful [63]. Nevertheless, a meta-analysis of two large clinical trials has shown that the

vaginal administration of micronized progesterone improves results in women with vaginal bleeding during pregnancy and a history of one or more miscarriages [17]. The effectiveness of progesterone treatment positively correlated with the number of subsequent losses [15].

Autoimmune disorders

Antiphospholipid syndrome.

Antiphospholipid syndrome (AFS) is an acquired thrombophilia associated with antiphospholipid antibodies. AFS is the most common curable cause of recurrent miscarriage [47] and is diagnosed in 15-20% of women with recurrent miscarriage [31, 32]. AFS is characterized by vascular thrombosis and/or obstetric complications, including early and late miscarriages (<20-24 weeks of pregnancy) and third trimester complications such as preeclampsia, premature birth and fetal growth restriction. Miscarriage is the most common complication of obstetric AFS, which by definition is present in women with a positive test result for antiphospholipid antibodies, and also has obstetric complications, including repeated fetal loss, stillbirth, fetal growth retardation or preeclampsia [38], occurring in 38.6% of women with AFS in one European study [2]. There is no difference in the prevalence of AFS among women with two or three or more losses [17].

Antibodies to the thyroid gland. Some studies have shown that antibodies to the thyroid gland (thyroglobulin, antithyroperoxidase and antibodies to thyroid-stimulating hormone receptors) are more common in women with repeated pregnancy loss than in the general population, even in the absence of thyroid dysfunction [15]; however, it is unclear whether antibodies to the thyroid gland cause repeated pregnancy loss [16]. Given this uncertainty, one systematic review and meta-analysis concluded that there is no evidence to support routine testing of women with repeated pregnancy loss for thyroid autoimmunity [18]. The mechanisms by which antithyroid antibodies can cause repeated pregnancy loss are unknown, although it was assumed that antithyroid antibodies can cause a slight deficiency of thyroid hormones, which may worsen decidualization [29]. However, the absence of an obvious link between intersubclinical hypothyroidism and repeated pregnancy loss seems to refute this assumption [17].

Endocrine factors

Thyroid function.

Overt hypothyroidism is a known risk factor for miscarriage and impaired neurocognitive development of the fetus. On the contrary, subclinical hypothyroidism does not increase the risk of repeated pregnancy loss.

Polycystic ovary syndrome. Polycystic ovary syndrome (PCOS), according to the Rotterdam criteria, requires the presence of two of the following three disorders: oligoovulation (irregular ovulation) or anovulation (lack of ovulation), hyperandrogenism and/or the presence of polycystic ovaries on ultrasound [34]. PCOS has been associated with a range of pregnancy complications, including fetal loss, gestational diabetes mellitus and preeclampsia; however, these disorders may be associated with concomitant PCOS diseases (obesity, metabolic syndrome, hyperinsulinemia or hyperandrogenism). and not directly to PCOS. Indeed, there is no clear evidence that PCOS is an independent risk factor for repeated pregnancy loss. The prevalence of PCOS in women with repeated pregnancy loss is similar to the prevalence among the general population, and PCOS status also does not affect the

prognosis of repeated pregnancy loss [17].

Obesity. Obesity (BMI ≥ 30 kg/m²) is an independent risk factor for repeated pregnancy loss [5], [12]. Women with obesity and recurrent pregnancy loss are more likely to have euploid miscarriages than women without obesity [7]. Obesity is associated with many endocrine disorders, including PCOS, hypothyroidism and diabetes mellitus; however, as mentioned earlier, many of these concomitant diseases individually did not demonstrate a convincing connection with repeated pregnancy loss [17]. Emerging data indicate that obesity affects the endometrium (for example, impaired decidualization and invasion of trophoblasts in mice with diet-induced obesity) [50]. In addition, obese women have fewer average luteal eMSCs [44] and increased accumulation of glycosylation end products in the endometrium, which worsens decidualization and inhibits trophoblast invasion in vitro [3]. Obesity is strongly associated with over-infertility, at least in the context of recurrent pregnancy losses [6].

Vitamin D deficiency. There is insufficient clinical data confirming the link between vitamin D deficiency and recurrent pregnancy loss [21]. Vitamin D deficiency is common in women trying to get pregnant [13] and is usually treated because of its modest but significant effect on fertility and live birth rates [43]. The mechanism by which vitamin D deficiency can be associated with miscarriage is unclear, although it is assumed that vitamin D deficiency can increase the concentration of autoantibodies, including antiphospholipid and antithyroid antibodies [45].

Hereditary thrombophilia. Thrombophilia is an acquired or hereditary disease that affects blood clotting and increases the risk of developing venous or arterial thromboembolism. Thrombophilia is caused by single mutations, such as in F5 (coding factor V Leiden) or F2 (coding factor II), or multiple mutations that lead to a deficiency of protein C, protein S and antithrombin. Although early studies have shown an association between repeated pregnancy loss and hereditary thrombophilia, more thorough analyses have not confirmed these associations [9, 42].

Conclusion. The prognosis of future pregnancy depends on the presence of embryonic genetic anomaly, intrauterine infection, structural defect, gestational trophoblastic disease or the underlying disease of the mother associated with miscarriage. This is of great clinical importance. It is necessary to distinguish between miscarriage of pregnancy of known etiology and those that are idiopathic. For example, genetic counseling may be recommended if one or both parents have a hereditary risk of miscarriage.

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Contact information:

Blushinova Ayaulym N. - Ph.D. candidate at the NCJSC “Semey Medical University”, Semey, Republic of Kazakhstan

Postal address: Republic of Kazakhstan, Semey, Pervomayskaya street, 37

E-mail: ayaulym.blushinova@smu.edu.kz

Phone: +77781024787