World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-31, February 2024
ISSN: 2749-3644

NON-DEVELOPING PREGNANCY: THE MAIN CAUSES OF DEVELOPMENT AND RISK FACTORS

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Article history:

Received: December 4th 2023
Accepted: January 4th 2024
Published: February 6th 2024

Abstract:

Non-developing pregnancy is a special form of pregnancy failure in which the embryo (foetus) dies in the early stages of gestation.
The most common causes of undeveloped pregnancy are chromosomal abnormalities, poor lifestyle, infectious factors, including sexually transmitted infections, genetic mutations and uterine abnormalities, maternal endocrine and immunological disorders and chronic endometritis. Ignoring or insufficiently considering possible aetiological factors and conditions contributing to miscarriage increases the risk of recurrent reproductive losses.

Keywords: non-developing pregnancy, undeveloped pregnancy (UP), miscarriage, causes of development, risk factors

RELEVANCE

Miscarriage is one of the urgent problems of practical obstetrics due to its social and medical significance. According to literature data, its frequency in the structure of reproductive losses is quite high and varies between 24.5 – 28.6% and in the cases of first trimester miscarriages it is 45 – 88.6% and does not tend to decrease.

AIM OF THE STUDY

To study various risk factors and causes of foetal death in early foetal development and to assess their impact on future reproductive function.

MATERIALS AND METHODS OF THE STUDY. Under observation were 35 patients with a verified diagnosis of UP treated in the gynaecological department of the maternity hospital No. 2 in Samarkand city.

RESULTS AND DISCUSSION.

Women with UP aged 25 to 35 years accounted for 62% of cases. According to the nature of their labour activity, more than half of the female patients with UP worked in state institutions. Non-working women accounted for 23.3 per cent of cases. Heavy physical labour was noted in 5.7% of women with UP. The mean age of sexual debut was 18 ± 2.1 years. 26.6 per cent of women were first-pregnant with UP, and recurrent UP was noted in 22.85 per cent of patients. In 60 per cent of first-pregnant women, the first pregnancy ended in a medical abortion. The actual pregnancy was accompanied by exacerbation of chronic herpetic infection in 14% of the patients and acute respiratory viral infection occurred in 11% of the women. Sixty per cent of pregnant women were admitted with the clinic of threatened or incipient miscarriage. The leading clinical signs were bloody discharge of varying intensity and pain. This was an indication for pregnancy-preserving therapy in the majority of women. In 20% of women, the intensity of uterine bleeding required urgent uterine scraping.

In 31% of patients there were no subjective symptoms, and an undeveloped pregnancy was diagnosed by ultrasound at the antenatal clinic. These patients were routinely admitted for uterine scraping.

In 71% of cases, the diagnosis of UP was confirmed by ultrasound, the indication for which was the ineffectiveness of preservation therapy, uterine size mismatch with gestational age. In the first trimester, 34 (97.1%) women had an undeveloped pregnancy, and 1 (2.9%) in the second trimester of pregnancy. According to ultrasound findings, UP at 5-6 weeks' gestation was 34.6 per cent of cases, in 7-8 weeks it was 46.0 per cent. There were 1 case each of UP at 12-13 weeks' gestation and at 16 weeks' gestation. Thus, the death of the foetal egg mostly occurred before the 8th week of gestation.

LITERATURE REVIEW

Failed miscarriage (undeveloped pregnancy, failed abortion, frozen pregnancy) is understood as intrauterine death of the embryo (foetus) that is not accompanied by its spontaneous "expulsion" from the uterine cavity with its delay for an indefinite period of time. In the IARMS guidelines on undeveloped pregnancy, this pathology is considered as a pathological symptom complex, including: 1) non-viability of the foetus (embryo);
2) pathological inertness of the myometrium;
3) disorders in the haemostasis system.
All the variety of factors leading to pregnancy loss are combined into three main groups:

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1. Embryonic defects – chromosomal abnormalities and teratogenic disorders (ionising radiation, rubella, influenza, enterovirus infection, viral hepatitis, cytomegaly, pharmacological drugs), which prevent the development of the embryo.
2. Maternal – infectious, anatomical, endocrine, immunological, genetic changes in the maternal environment.
3. Paternal – factors determining the inferiority of spermatogenesis.

Embryonic defects (chromosomal abnormalities and teratogenic disorders). One of the main causes of early term UP is the genetic factor. Up to 95% of chromosomal and genomic mutations lead to termination of pregnancy at different terms. UP can be caused by chromosomal anomalies, genetic mutations and hereditary predisposition. Quantitative chromosomal changes (aberrations) play a special role in the etiology of UP. Among chromosomal aberrations, the largest group of chromosomal anomalies associated with miscarriages are autosomal trisomies and the frequency of this phenomenon increases with the age of the mother. The most common and well-known variant are trisomies: on the 21st chromosome – Down syndrome, on the 13th chromosome – Patau syndrome, on the 18th chromosome – Edwards syndrome. The most common single chromosomal abnormality is karyotype 45, X. Monosomy X occurs in 20-25% of observations with karyotype pathology. Approximately 20% of genetic anomalies are triploidy and 5% are tetraploidy. The older the age of the mother, the higher the risk of aneuploidy, a karyotype change in which the number of chromosomes is not a multiple of 23. (> 30% in people aged 40 years).

Qualitative chromosomal aberrations are more often represented by translocations in one of the partners. Of particular interest are situations in which the embryo's karyotype is normal, but there is fetal arrest due to mutations at the gene level, such as mutations of DNA microsatellite loci.

Teratogenic and mutagenic factors may also play a role in spontaneous abortion, but their quantification is difficult. Risk factors for the development of chromosomal aberrations in human embryos may include chemical (mutagens), physical (irradiation, temperature shock) and biological (gamete overripening, viral infections) exposures, and drug administration.

Maternal factors (infectious, anatomical, endocrine, immunological, maternal genetic changes).

Many scientists note that a significant role in women with failure of pregnancy play endocrine factors . These include:

hyperandrogenic conditions, including polycystic ovary syndrome and congenital dysfunction of the adrenal cortex; hyperprolactinaemia; insufficiency of the luteal phase of the menstrual cycle; thyroid diseases; diabetes mellitus.

The frequency of endocrine factors averages 17%, although there is evidence of endocrine disruption in some groups with non-pregnancy. There is abundant evidence Of the association of embryo death with endocrine Abnormalities leading to luteal phase insufficiency and, consequently, functional fullness of the endometrium – the range of statistics in the literature is quite wide –

from 8-20% to 30-78.2% . In numerous studies, among the factors leading to perinatal pathology and antenatal fetal death, the role of hyperandrogenism of various genes is high.

According to a number of authors, the incidence of pregnancy failure in the first trimester due to hyperandrogenism is 21-32%. Of these, hyperandrogenism of adrenal origin is present in 30%, ovarian origin in 12.1 per cent and mixed in 57.9 per cent of women with undeveloped pregnancy. For patients with hyperandrogenism (HA) of different genesis, more than 50 per cent of pregnancies are terminated in the first trimester, with every third woman having an UP of the embryo death type, in every fourth case anembryony is detected. Excess androgens lead to hypoestrogenism, which leads to the formation of luteal phase insufficiency . It is believed that testosterone inhibits myometrial contractility, which favours the persistence of the dead embryo in the uterine cavity, while the trophoblast continues to produce progesterone and β-hCG, which prevents the rejection of the foetal egg.

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age.

Mild abnormalities of prolactin synthesis can lead to an undeveloped pregnancy. 40% of women with hyperprolactinaemia are observed impaired secretion and metabolism of androgens, they are noted increased content of dihydroepiandrosterone and dihydroepiandrosterone sulphate, decreased sex steroid binding globulin, which manifested by insufficient decidualisation of the embryonic membranes. The most common clinical signs of hyperandrogenism are absent.

Primary hypothyroidism accompanying autoimmune thyroiditis is considered a risk factor for pregnancy termination as a risk factor for pregnancy termination due to the stimulating effect of thyroid hormones on the function of the corpus luteum, which plays a major role in the maintenance of early pregnancy. There is evidence that thyroid dysfunction and autoimmune

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thyroid diseases are associated with infertility and pregnancy failure, both in the presence of antibodies to thyroid tissue and without their detection in the presence of elevated thyroid hormone levels.

According to a study by foreign authors, the presence of antibodies against thyroperoxidase (TPO-Ab) increases the risk of sporadic miscarriage. In numerous studies by domestic and foreign authors, autoimmune thyroiditis is a marker of autoimmune disadvantage and may lead to the development of antiphospholipid syndrome.

Often the death of the embryo (foetus) occurs in the presence of diabetes mellitus in the mother, which dictates at the need to prepare for the planned pregnancy.

When studying the role of immunological factors in the clinic of miscarriage of pregnancy, two groups of disorders were identified: humoral and cellular immunity. Disorders in the humoral immunity link are associated with antiphospholipid syndrome. The second, no less complex mechanism of pregnancy failure is caused by disorders in the cellular immunity, which is manifested by the response of the mother's body to the paternal antigens of the embryo, due to the compatibility of the spouses according to the HLA system. According to some reports, up to 10% of cases of UP are associated with systemic autoimmune conditions resulting in the formation of antiphospholipid antibodies (APA). This can develop into antiphospholipid syndrome (APS) – an autoimmune disease defined by the presence of thromboembolic complications or pregnancy complications in the presence of persistently elevated titres of APA. Some scientists have concluded that obstetric pathology as well as neurological complications in APS cannot be explained by ischaemia and thrombosis alone . The results of some studies suggest that the pathophysiology of spontaneous abortion in APS patients is most likely related to inflammation of the chorion/placenta and disruption of normal trophoblast function rather than prothrombotic events.

A special risk group includes women with anomalies of the anatomical structure of the uterus.The uterine factor of non-developing pregnancy is represented by malformations of the genital apparatus, genital

Infantilism, intrauterine synechiae, uterine myoma, endometrial polyp, isthmic and cervical insufficiency. The most common pathology of congenital uterine defects in women with UP is bicornuate uterus (37%), partial or complete intrauterine septum (22%), saddle-shaped (15%). Acquired anatomical defects include submucosal uterine myoma, intrauterine synechiae, and isthmic-cervical insufficiency. According to Abashov E.I. (1999) uterine myoma occurs in 15% of patients with UP. Another pathological condition characterised by the formation of adhesions and connective tissue fusions of the endometrium with sclerosis and fibrosis of its stroma is Asherman syndrome. Asherman's syndrome develops in approximately 40% of patients who have undergone dilatation and curettage for an undeveloped pregnancy, and in one in four (25%) of those who have undergone these manipulations for any reason within 1-4 weeks after delivery. According to Sayfiddinova F.A. (2012), Asherman syndrome is an incidental finding in 12-15% of women with habitual pregnancy failure. Currently, chronic diseases characterised by asymptomatic recurrent course prevail among pelvic inflammatory diseases.

In UP, opportunistic microorganisms were detected in 20% of patients, and viral-bacterial associations in 70%. These results are consistent with the data of other scientists, according to the studies of which more than 64% of UP causes have persistence of urogenital infection, causing the development of infectious-inflammatory process in the uterine cavity, disturbance of homeostasis in the gravidar endometrium and embryo microenvironment. In almost half of women endometrial dysfunction is not due to inflammation, but to the progressive syndrome of reconstructive-plastic failure, the result of which is atrophy of the uterine mucosa. This process in various tissues and organs, including the female reproductive system, is based on the depletion of regenerative potential. It is known that changes in the state of the haemostasis system, detected in 30-50% of patients with habitual miscarriage of pregnancy, largely determines the course and outcome of pregnancy for mother and foetus. According to various authors, genetic forms of thrombophilia among the causes of pregnancy loss account for 10-30%. Currently, there is no doubt that antiphospholipid syndrome plays a leading role in the structure of thrombosis due to disorders of the haemostasis system.

According to different authors, this syndrome is diagnosed from 3-5% to 27-42% of cases in patients with habitual miscarriage. After embryo death, the level of hCG, secreted by chorion cells and stimulating steroidogenesis in the corpus luteum, decreases. The syncytiotrophoblast remains viable and functionally active for the longest time, with which the secretion of hormones and immunosuppressive peptides that inhibit the contractile activity of the uterus is associated. Continued production of progesterone by the trophoblast in UP prevents rejection of the foetal egg and the onset of miscarriage.

Paternal factors.

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As a separate factor in the development of abnormal pregnancy, the so-called male factor (male factor) – disorders arising in the process of spermatogenesis. Meta-analysis of data from 16 large-scale studies showed that a high level of DNA fragmentation in paternal sperm significantly increases the risk of spontaneous abortion.

Risk factors.

Socio-dependent lifestyle and nutritional factors influence reproductive health and disease. A meta-analysis of data from several studies showed that women with a body mass index >25 kg/m2 were at greater risk of spontaneous abortion. In another paper analysing data from 6 large-scale studies (about 30 000 pregnancies), it was shown that a BMI greater than 28-30 kg/m2 significantly increased the risk of spontaneous miscarriage.

Regression analysis showed that increased BMI is the second most significant factor for increased risk of miscarriage after age. In industrial cities and large population centres miscarriage are statistically higher than in small settlements. A direct correlation between pregnancy termination and the mother's occupation, the nature of her labour (standing, vibration, heavy lifting), the presence of occupational hazards (contact with dyes, petrol, insecticides). Davor J. and Overton C. believe that in pregnant women under 35 years of age, the risk of UP is 15%, while the risk of UP in pregnant women under 35 years of age is 15%, so in 35-39 years is 25% and in 40-44 years increases to 51%, in 45 and more reaches 90% of cases. Klechan M.M. considers the age of the pregnant woman under 18 years as a risk factor for not carrying a pregnancy, and Kuznetsova O.A. (2013) refers to the risk group of first-pregnant women.

CONCLUSIONS.

Thus, according to the results of the study, the risk factors for the development of UPwere as follows: early age of sexual debut, termination of the first pregnancy by medical abortion, and a history of pelvic inflammatory diseases. Acute respiratory viral infections in early pregnancy, as well as a high percentage of pregnant women infected with herpes simplex virus reflect the role of the infectious factor in the death of the embryo in early pregnancy.

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Volume-31, February 2024
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