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MISCARRIAGE AND PREMATURE BIRTH

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Annotation:
The problem of protecting the health of mother and child is considered as the most important component of health care, which is of paramount importance for the formation of a healthy generation of people from the earliest period of their life. Among the most important problems of practical obstetrics, one of the first places is occupied by miscarriage and premature birth.

Key words: high-risk pregnancy, preterm delivery, management, prevention, antiphospholipid antibodies (APA); antiphospholipid syndrome (AFS); miscarriage; plasmapheresis; TORCH infections.

The frequency of miscarriage is 10-25% of all pregnancies, 5-10% - preterm birth. Premature babies account for over 50% of stillbirths, 70–80% of early neonatal mortality, and 60–70% of infant mortality [1, 5, 12]. Premature babies die 30-35 times more often than full-term babies, and perinatal mortality in miscarriage is 30-40 times higher than in term births. Let's take a look at the terms:
Miscarriage - spontaneous termination of pregnancy at various times from conception to 37 weeks, is considered from the 1st day of the last menstruation to 259 days from this date.
According to the World Health Organization, preterm births are defined as births between 22 and 37 completed weeks of gestation, counting from the first day of the last menstrual period, with a fetal weight of 500 g or more.
The most common causes of miscarriage are: endocrine disorders of the reproductive system; erased forms of adrenal dysfunction; damage to the receptor apparatus of the endometrium, clinically manifested as an incomplete luteal phase; chronic endometritis with persistence of opportunistic microorganisms and/or viruses; isthmic-cervical insufficiency (ICN); malformations of the uterus; intrauterine synechia; antiphospholipid syndrome and other autoimmune disorders.
The survey is carried out in a certain sequence:
1) general clinical examination, exclusion of genital infections: chlamydia, ureaplasma, mycoplasma, gonorrhea, trichomonas. Determination of the vaginal

flora and its sensitivity to antibiotics, IgG and IgM in the blood to chlamydia, mycoplasma and ureaplasma;
2) TORCH-complex: detection of IgG and IgM antibodies to rubella, toxoplasma, HSV types 1 and 2, CMV;
3) hysterosalpingography in the 2nd phase on the 18th-22nd day with a 28-day cycle or on the 4th-6th day of the rise in rectal temperature to exclude anatomical changes in the pelvic organs, synechia in the uterine cavity, isthmic-cervical insufficiency;
4) Ultrasound of the pelvic organs assesses the condition of the ovaries (polycystic ovaries, cysts, and other formations), endometrium (chronic endometritis, endometrial hyperplasia, endometrial thickness before ovulation, and other features of the endometrium), myometrium (uterine fibroids, adenomyosis);
5) hysteroscopy, endometrial endometrial scraping or separate diagnostic curettage (RDV) of the uterine mucosa;
6) hormonal studies - carried out on the 2nd-5th day of the cycle, the level of LH, FSH, prolactin, testosterone, dehydroepiandrosterone, radiol est is determined; on the 22-23rd day of the cycle or better on the 4th day of the rise in rectal temperature, the level of progesterone is determined;
7) determination of antibodies to chronic human gonadotropin (hCG), anticardiolipin antibodies and other autoimmune disorders, since 27% of patients have autoimmune disorders;
8) genetic examination (chromosomal karyotyping of both parents);
9) histocompatibility of spouses (according to the H1_A system).
Anatomical causes of miscarriage
The frequency of anatomical anomalies in patients with miscarriage ranges from 10-16%:
- congenital anomalies in the development of the uterus (complete doubling of the uterus, bicornuate, saddle-shaped, unicornuate uterus, partial or complete intrauterine septum);
- acquired anatomical defects (intrauterine synechia - Asherman's syndrome, submucosal uterine fibroids);
- isthmic-cervical insufficiency.
Termination of pregnancy with anatomical abnormalities of the uterus may be associated with unsuccessful implantation of the fetal egg (often on the intrauterine septum, near the submucous node of the uterus), insufficiently developed vascularization and endometrial reception, and close spatial relationships.

The anatomical causes of miscarriage include CI, recognized as the most common etiological factor in abortion in the second trimester. The frequency of occurrence is 13-20% among patients with miscarriage.

Women at high risk for developing CCI may include:

- over 30 years old, obese or overweight, with a history of late spontaneous miscarriages or premature births;
- who have undergone two or more intrauterine interventions with the expansion of the cervical canal or who have undergone invasive methods of treating cervical pathology (that is, a history of cervical trauma - post-traumatic CCI);
- with polycystic ovary syndrome (PCOS), hyperandrogenism, chronic endometritis, infertility and those who have this pregnancy as a result of IVF;
- with connective tissue dysplasia, increased levels of relaxin in the blood serum (with multiple pregnancies, ovulation induction by gonadotropins);
- with congenital malformations of the uterus.

These patients should be carefully examined at the stage of pregnancy planning and be under special supervision in order to prevent late spontaneous miscarriages and premature births (Tkachenko L.V., Linchenko N.A., 2014).

Diagnosis of CCI outside of pregnancy

It is necessary to include in the examination of patients with CI at the stage of pregnancy planning, in addition to the generally accepted bacteriological examination and examination of the hormonal background, metrosalpingography and, if possible, a pipel biopsy with immunohistochemical examination of the endometrium (Tkachenko L. V., Linchenko N. A., 2014).

Hysterosalpingography is performed on the 18-20th day of the menstrual cycle to determine the state of the internal os, and if it is expanded by 6-8 mm, this is regarded as an unfavorable prognostic sign. To differentiate the type of cervical insufficiency, patients need to undergo metrosalpingography using a progesterone test (Melnikova S. E. et al., 2006; Sidelnikova V. M., 2010).

A differentiated approach to the correction of CI during pregnancy consists in suturing the cervix at 12-14 weeks of gestation in patients with anatomical form of CI and conducting progestogen therapy (duphaston 10 mg 2 times a day or utrogestan 200 mg 2 times a day) up to 34 weeks pregnancy.

In patients with a dysfunctional form of ICI, therapy with Proginova 1 tablet 2 times a day should be carried out until 5-6 weeks of pregnancy, duphaston 10 mg 2 times a day or utrogestan 200 mg 2 times a day from 5-6 weeks to 34 weeks of pregnancy. If a shortening of the cervix is detected, this therapy should be supplemented with the introduction of an obstetric pessary.

Due to the fact that it is recommended to take gestagens up to 34 weeks of pregnancy, it is necessary to take informed consent from the patient.

In case of ICI correction with an obstetric pessary, cervicometry with a vaginal probe should be performed once every 10 days. With progressive shortening of the cervix (up to 2.5 cm or less) or opening of the internal os (up to 8 mm or more), perform suturing on the cervix (Tkachenko L. V., Linchenko N. A., 2014).

The sutures are removed at 37-38 weeks of pregnancy.

Preparing for pregnancy in patients with intrauterine synechia consists of 2 stages:

- preparation for surgical treatment - electrophoresis of longidase, lidase, ronidase (perhaps intramuscular injection), suppositories with ronidase, Wobenzym are prescribed;
- surgery - dissection of synechia during hysteroscopy. It is advisable to introduce a spiral after surgery and conduct cyclic hormone therapy (femoston 2/10, cycloprogen), metabolic therapy for 3 cycles. After 3 cycles, the spiral is removed and another 2-3 cycles of cyclic hormonal and metabolic therapy are performed.

When making a diagnosis of "uterine fibroids" of any localization that interferes with pregnancy, it is necessary to resolve the issue of myomectomy.

Access to surgical intervention is decided individually. Laparotomy, laparoscopy, resectoscopy are possible, after which rehabilitation measures are carried out for six months, including hormone therapy, physiotherapy treatment (FTL). A year later, with a wealthy scar on the uterus, pregnancy is allowed.

Genetic factors in the structure of miscarriage - 3-6%.

Spontaneous miscarriages due to chromosomal abnormalities are more common in families in which there have already been cases of miscarriage or infertility, and also if one of the parents has already had children with congenital malformations or children with mental retardation.

Valuable information for the diagnosis of fetal chromosomal abnormalities is the cytogenetic analysis of abortus.

To find out if a genetic factor is the main cause of a miscarriage, it is necessary to study the karyotype of both parents. If a pathology is found in the karyotype of a married couple, a consultation with a geneticist is necessary.

Endocrine causes of miscarriage

These causes range from 8 to 20%, the most significant of them are: luteal phase insufficiency (LFP); thyroid dysfunction; hyperandrogenism (ovarian, adrenal and mixed genesis); diencephalic pathology; diabetes.

An inferior luteal phase is found in 85% of patients with recurrent pregnancy loss according to functional diagnostic tests.

Reasons for the formation of NLF in patients with miscarriage:
1) hormonal disorders;
2) damage to the receptor apparatus of the endometrium;
3) the presence of chronic endometritis.
Tactics of preparation for pregnancy
Cyclic hormonal therapy for 2-3 cycles under the control of rectal temperature graphs, a combination of 2 mg of micronized 17p-estradiol and 10 mg of dufaston, from the 12th-14th day of the progestogen cycle for 3 menstrual cycles.
In the absence of pregnancy after 2-3 cycles
Against the background of cyclic hormonal therapy - stimulation of ovulation with clostilbegit, at a dose of 50 mg 1 time per day from the 5th to the 9th day of the cycle for 1 cycle, in the absence of pregnancy, increase the dose with clostilbegit, increase to 100 and 150 mg / day.
Tactics of pregnancy management
Taking gestagens orally or vaginally up to 16-20 weeks of pregnancy. Courses of metabolic therapy, taking antihypoxants, antioxidants. Pro-
prevention of placental insufficiency from the first trimester of pregnancy.
With NLF, there is always a failure of the endometrial receptor apparatus.
Stimulation of the receptor apparatus of the endometrium: acupuncture, magneto-laser therapy (Rik-ta, Quanterra), copper electrophoresis - 15 sessions from the 5th day of the cycle. Cyclic hormone therapy (with an excess of hormones, the sensitivity of the receptor apparatus increases). Complexes of metabolic therapy.
When pregnancy occurs, hCG is recommended at a dose of 5000 IU 2 times a week for up to 10-12 weeks under the control of the hCG level, which stimulates the production of steroid hormones, increases the receptivity of the endometrium, and promotes decidualization. Prevention of placental insufficiency from the first trimester of pregnancy.
Miscarriage in the presence of chronic endometritis
The inflammatory reaction leads to the activation of local immune responses in chronic endometritis. In this regard, prothrombinase is activated, which contributes to thrombosis, heart attacks, and detachment of the trophoblast. This situation leads to a violation of the processes of placentation, invasion and development of the chorion - termination of pregnancy.
Preconception preparation
An individually selected set of preventive and therapeutic measures: antibiotics, antimycotics, systemic enzyme therapy, immunomodulating agents, interferon inducers, rehabilitation therapy for PTL (electrophoresis with Cu, Zn, magneto-laser

therapy, mud therapy, etc.). Gestagen support in the second phase of the menstrual cycle for 2-3 months (dydrogesterone 20 mg per day per os or micronized progesterone vaginally 400 mg/day).

Upon the onset of pregnancy, the continuation of gestagenic support from the moment of a positive pregnancy test. Since with a low level of progesterone and low sensitivity of receptors, PIBF is not produced enough, and therefore there is no formation of immunotolerance, a high level of pro-inflammatory cytokines and NK cells is maintained.

Antiphospholipid syndrome (APS) remains a generally recognized autoimmune condition leading to embryo/fetal death. The frequency of APS in the population reaches 5%, among patients with recurrent miscarriage APS is 27-42%.

The term "antiphospholipid syndrome" refers to a group of autoimmune disorders characterized by a significant amount of antibodies to the phospholipids contained in the blood plasma (antiphospholipid antibodies), as well as to the glycoproteins associated with these phospholipids, clinically manifested by thrombosis or increased blood clotting in vessels of any caliber.

Clinical criteria for APS include: a history of vascular thrombosis; three spontaneous miscarriages or more for a period of 10 weeks, when the anatomical, genetic and hormonal causes of miscarriage are excluded; one death of a morphologically normal fetus or more for up to 10 weeks of pregnancy; one premature birth or more at 34 weeks due to severe preeclampsia or severe placental insufficiency.

Laboratory Criteria

Average or high titer of anticardiolipin antibodies in the study by the standard enzyme immunoassay in two or more samples taken with an interval of 6 weeks; the presence of lupus anticoagulant in plasma in two studies or more, made with an interval of 6 weeks.

The diagnosis of antiphospholipid syndrome is made in the presence of one clinical and one serological criterion.

Management algorithm for patients with antiphospholipid syndrome before pregnancy: normalization of hemostasis; correction of the immune status (antiviral immunomodulatory therapy, since most patients with APS are carriers of herpes simplex virus, cytomegalovirus, Coxsackievirus types A and B, enteroviruses).

During pregnancy:

- glucocorticoids 5-10 mg, dose selection taking into account the activity of the lupus anticoagulant. Reception of glucocorticoids begins from the middle of the fertile cycle, continues throughout pregnancy and two weeks postpartum;

- performing a hemostasiogram every 2 weeks until 12 weeks of pregnancy, then every 3-4 weeks until the end of pregnancy;
- individual selection of doses of antiplatelet agents, anticoagulants, if necessary - plasmapheresis;
- three courses of immunoglobulin therapy at 7-8 weeks, 24 weeks and before delivery;
- assessment of the state of the fetoplacental complex - ultrasound, cardiotocography (CTG), doplerometry and prevention of placental insufficiency;
- performance of a control hemostasiogram on the 3rd-5th day after childbirth (danger of thromboembolism), lower doses of antiplatelet agents, gradual withdrawal of glucocorticoids.

The preterm birth syndrome is multifactorial. However, the analysis of the mechanisms of development of preterm labor allows us to identify four main causes of preterm labor: infection, maternal and/or fetal stress caused by extragenital pathology, complications of pregnancy and placental insufficiency, thrombophilic disorders, and uterine hyperextension in case of multiple pregnancies.

Premature births are called those that occur during pregnancy from 22 (22/0) to 37 (36/6) weeks (259 days), starting from the first day of the last normal
small menstruation with a regular menstrual cycle, while the weight of the fetus is from 500 to 2500 g, and the growth of the fetus is from 25 to 45 cm.

Medical care in these cases (including neonatal resuscitation) should be provided in full in an obstetric hospital.

As the analysis of the literature shows, in 40-50% of cases, the cause of preterm birth cannot be established.

Currently, all treatment of the threat of interruption is reduced to symptomatic treatment - the use of funds to reduce the contractile activity of the uterus. This explains why, with a huge number of different tocolytic agents in the available arsenal, the frequency of preterm birth in the world does not decrease, and the decrease in perinatal mortality is mainly due to the success of neonatologists in nursing premature babies.

Risk factors for preterm birth (PR) are divided into anamnestic (relating to past pregnancies) and concomitant of this pregnancy. Due to the large number of factors, distribution by risk groups (forecasting) for PR is difficult, although special scales have been developed for this.

Anamnestic: 1 or more PR in history (increased risk by 2.5 times); 2 or more curettage of the uterine cavity (including during artificial abortions); Conization / amputation of the cervix; Systemic connective tissue diseases (Ehler-sa-Danlo, Marfan syndrome, systemic lupus erythematosus).

Socio-medical reasons: smoking; low socio-economic standard of living; low body mass index (BMI < 19.8) - malnutrition; obesity; stressful situation at work and / or in the family, chronic stress, depression; age < 18 or > 35 years; the interval between pregnancies is less than 6 months; multiple pregnancy; polyhydramnios or oligohydramnios; induced pregnancy; isthmic-cervical insufficiency; severe extragenital pathology - decompensation; urinary tract infection (including asymptomatic bacteriuria); placenta previa.

The pathogenesis of preterm labor is not fully understood, but it is known that they occur as a result of pathological processes or idiopathic early activation of labor.

Currently, preterm birth is considered to be a syndrome, which involves such mechanisms as infection (inflammation), decreased uterine and placental blood flow (placental hemorrhages), uterine hyperdistension, stress, and various processes mediated by the immune system.

During pregnancy, the myometrium is in an inactive state, which is ensured by the action of progesterone. For the development of uterine contractions, activation of the myometrium is necessary.

There is now increasing evidence that the biosynthesis and activity of prostaglandins are regulated by cytokines. The leading role of cytokines in the regulation of labor activity is confirmed by data on their influence on the effectiveness of the relaxing effect of progesterone. When the expression of pro-inflammatory cytokines, COX-2 (the most important source of prostaglandins) is activated, the sensitivity of the myometrium to the relaxing effect of progesterone decreases, and oxytocin receptors are formed.

Powerful stimulators of contractile activity of the myometrium are prostaglandins E2 and F2a, which are produced in the amnion, chorion, decidua and myometrium.

During childbirth, anti-inflammatory cytokines that normally suppress prostaglandin activity during pregnancy (TGF-p, IL-1 RA, IL-4, IL-10) may change their function during childbirth and activate prostaglandin synthesis in some tissues. Such a change in the function of anti-inflammatory cytokines during childbirth or a decrease in their activity was probably developed during evolution to ensure the normal activation of the inflammatory process necessary for physiological childbirth. An important role in the initiation of the process of childbirth is played by inflammatory decidual activation. The process is formed due to the embryonic-decidual paracrine system (synthesis and release of proteases) against the background of a decrease in the concentration of progesterone. In most cases, decidual activation occurs against the background of decidual bleeding (including partial placental abruption, thrombosis, etc.) or activation of intra-amniotic infection.

Thus, the activation of the inflammatory response underlies the initiation and regulation of the process of labor, both preterm and term. Deepening knowledge about the molecular mechanisms of labor induction will allow a complete revision of ideas about the physiology of childbirth.

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