

Pre-Course Training of Women With Reproductive Loss of Fetus in Anamnesis

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INTRODUCTION

Due to the widespread prevalence of reproductive losses, this problem is especially urgent today, remaining one of the leading in obstetrics. According to some scientists, reproductive losses are more often observed in young pregnant women - up to 20 years old or pregnant women over 30 years old.

According to various experts, up to 23% of diagnosed pregnancies end in spontaneous abortion. Thus, the problem of reproductive losses is not only a medical, but also a social problem (a decrease in population growth, an increase in the level of perinatal and child mortality, a negative impact on the reproductive function of women).

One of the priority areas of modern medicine is the study of the effect of extragenital diseases in women on the course of pregnancy and childbirth, on the development of the fetus and newborn, its adaptive capabilities, morbidity and mortality [2, 5, 10]. Violation of gestational restructuring of various systems of the maternal body in early pregnancy has different consequences and can lead to both the development of complications and reproductive losses in the absence of optimal conditions for the progression of gestation [1, 3, 4].

One of the complications of pregnancy requiring early delivery is reproductive loss of the fetus, which can manifest itself at different periods of gestation. The frequency of reproductive losses is quite high and ranges from 10 to 20%, in England - 2.8%, in the USA - 15%, in the CIS countries - 15-25%, in Uzbekistan - 16.4%. At the same time, the frequency of reproductive fetal loss in the first trimester is 68.6%, in the second - 21.3%, in the third - 10.1% [4, 5, 13]. Despite the significant progress achieved in antenatal protection of the fetus, in some cases, under the influence of various unfavorable factors, its intrauterine death occurs at different periods of gestation, which dictates the need for early delivery of a woman [14, 15, 17].

Reproductive loss in humans is about 50% in relation to the total number of conceptions. The frequency of miscarriage remains high, despite the progress achieved in the prevention and treatment of reproductive disorders in humans. At present, various types of spontaneous abortion are considered as multifactorial diseases [16, 18, 19], the development of which can be triggered by a combination of several factors. The individual contribution of each factor may be insignificant, and only their sum leads to the development of the disease. The causes of early embryonic loss are many and varied. Anomalies of the karyotype of the fetus are detected when the development stops and with a naturally occurring pregnancy, and with assisted

reproductive technologies.

Purpose of the study is to study the outcome of pregnancy depending on the performance of pre-gravid preparation in women with a history of reproductive losses.

MATERIALS AND METHODS

The study included 65 women who gave written informed consent to participate. The study was carried out prospectively by complex laboratory and instrumental examinations at the stage of pre-gravid preparation (Fig. 1) for pregnancy, which were divided into 2 groups.

Main group - 39 women, pregravid drug preparation was carried out for at least 3 months for the purpose of contraception (Yarina plus, Jess plus) before the onset of subsequent pregnancy, depending on the cause of reproductive loss of the fetus. Also, all pregnant women of the main group underwent drug prevention of placental insufficiency (PI) from early gestation.

Comparison group - 26 pregnant women who did not receive pre-gravid training.

Women of the main group at the pregravid stage and during gestation underwent a comprehensive laboratory and instrumental examination. Pregnant comparison groups underwent standard obstetric follow-up and examination at the local polyclinic. Women in the control group at the pregravid stage and during gestation underwent examination similar to the main groups.

For the effectiveness of pregravid preparation in women with a history of reproductive loss of the fetus for the contraception of COCs with folates (Yarina plus or Jess plus), despite etiological reasons, in order to prevent thrombotic complications and in case of insufficiency of the fetoplacental system, women were prescribed phlebotonics before and during pregnancy (Phlebodia 600mg) and L-arginine (Tivortin 100 ml IV drip followed by syrup according to the scheme).

Yarina plus, Jess plus is a low-dose monophasic combined estrogen-gestagenic contraceptive drug with auxiliary vitamins containing calcium levomefolate. The introduction of calcium levomefolate in the composition of an oral contraceptive drug reduces the risk of developing a neural tube of the fetus, fetal abnormalities, congenital malformations and, of course, the risk of anemia and micronutrient deficiency in both the mother and the fetus.

Phlebotonics (Phlebodia 600 mg) has a venotonic effect: it reduces the elasticity of the veins, increases the tone of the veins, reduces venous congestion, enhances the vasoconstrictor effect of adrenaline, norepinephrine. One tablet contains 600 mg of diosmin, which is the optimal daily dose for the venotonic effect. And also has - angioprotective effect: improves microcirculation; increases capillary resistance; reduces their permeability. Acts on the lymphatic system, i.e. improves lymphatic drainage, increases the tone and frequency of contraction of lymphatic capillaries, increases their functional density, reduces lymphatic pressure. In addition, it has a decongestant effect. Reduces the symptoms of inflammation (dose-dependent effect) and, most importantly, reduces the adhesion of leukocytes to the venous wall and their migration to paravascular tissues; improves oxygen diffusion and tissue

perfusion. Blocks the production of free radicals, the synthesis of prostaglandins and thromboxane.

LArginine is a conditionally essential amino acid; the average daily L-arginine intake is 5.4 g.

Table 1 The role of L-arginine (Tivortin) in the functioning of various body systems (Stepanov Yu.M. et al., 2004)

Functional systems of the body	Physiological reactions
The cardiovascular system	Relaxation of blood vessels of the brain, retina, heart, lungs, kidneys, intestines, cavernous tissue, heart muscles
Respiratory system, digestive and urogenital tracts	Relaxation of smooth muscle tissue of the trachea, stomach, intestines, urinary bladder, uterus
Central and peripheral nervous systems	Neuromodulatory activity that determines long-term potentiation, memory formation, pain perception, visual analysis
Hemostasis system	Regulation of the interaction of leukocytes with vascular walls. Regulation of platelet activity
The immune system	Antipathogenic reactions, nonspecific cytotoxicity, antitumor protection, pathogenesis of toxemias, transplant rejection

The physiological need of tissues and organs of most mammals for arginine is satisfied by its endogenous synthesis and / or intake with food, however, for young individuals and adults under stress or illness, this amino acid becomes essential (Table 4.1).

Arginine serves as a necessary precursor for the synthesis of proteins and many biologically important molecules such as ornithine, proline, polyamines, creatine and agmatine. However, the main role of arginine in the human body is to be a substrate for the synthesis of nitric oxide (NO) (Visek WJ, 1986; Wu G., Morris SM Jr., 1998; Böger RH, 2007).

To assess the effectiveness of pregravid preparation in the system of antenatal protection of the fetus, an analysis of the course of pregnancy in two groups of patients was carried out.

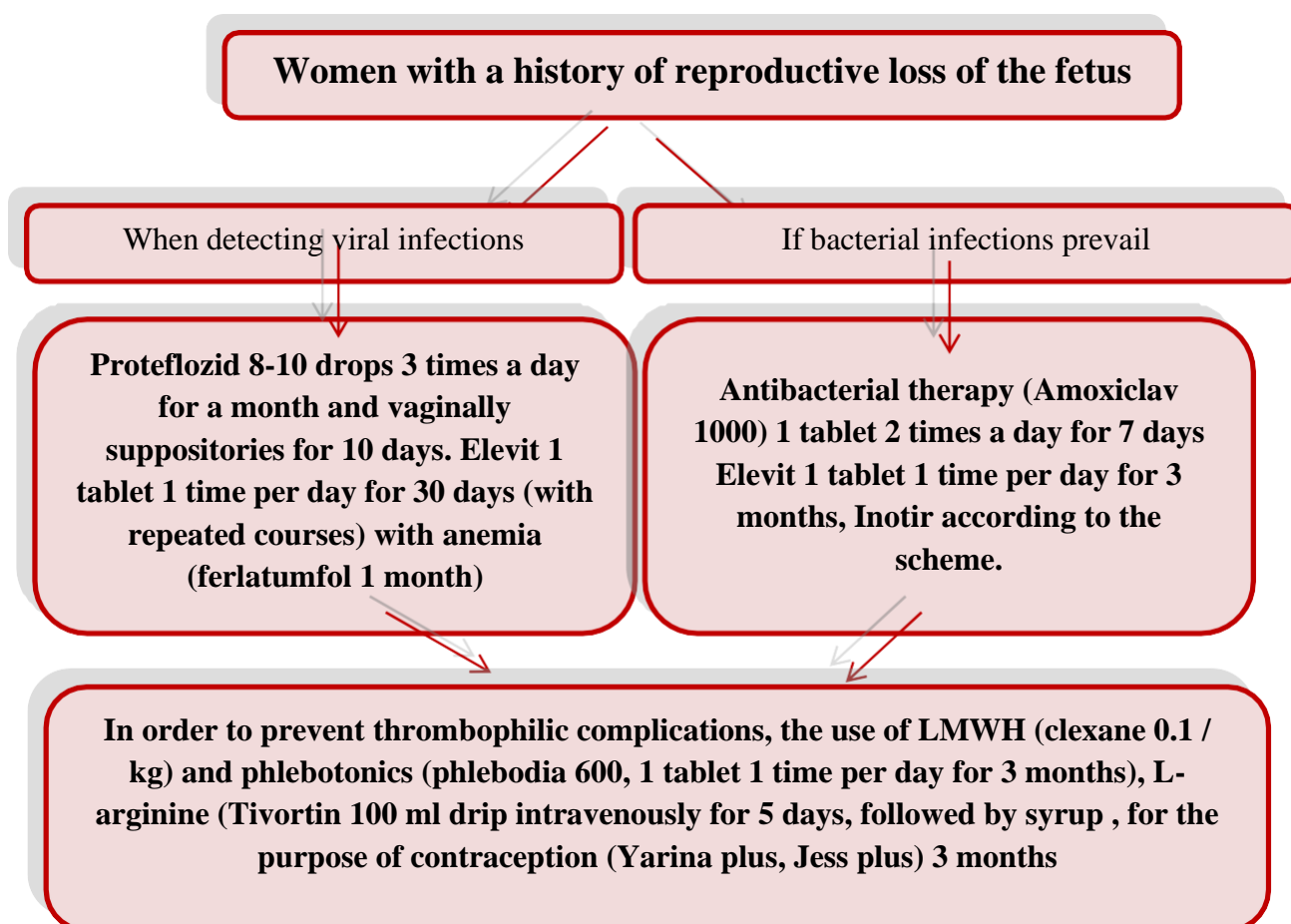


Figure: 1. Algorithm for pregravid training for women with a history of reproductive loss

RESULTS

The average age of women in the main group was 27.7 ± 4.8 years, in the comparison group - 28.4 ± 4.7 years, while 86% of women in the studied groups were in the age category from 20 to 34 years.

Analysis of the course of pregnancy showed that the incidence of complications at different periods of gestation, in particular, those that lead to the development of FPI and pose a risk of antenatal fetal death (threat of miscarriage, preeclampsia, chronic fetal hypoxia) was significantly higher in patients of the comparison group (Fig. 2).

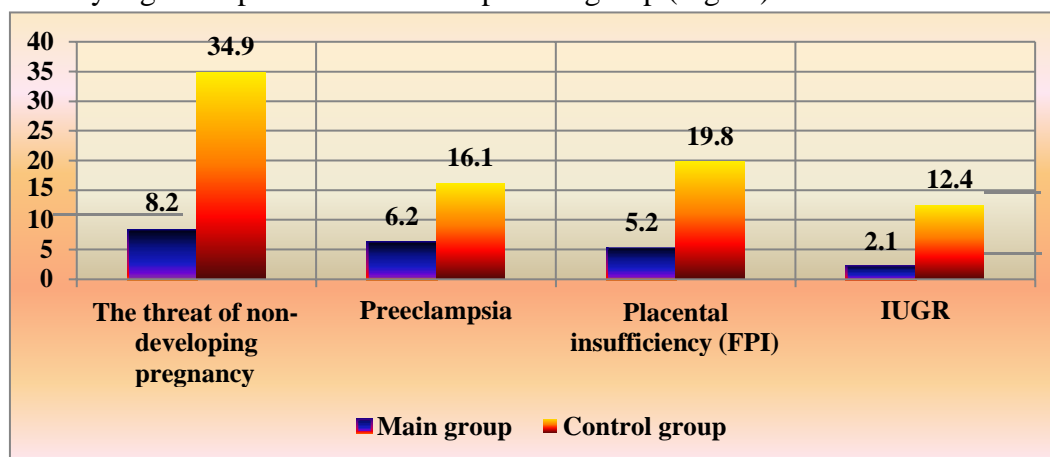


Fig. 2 Complications of pregnancy in observed patients

In the management of pregnant women in both groups, special attention was paid to identifying early signs of FPI. For this, the most modern methods for assessing the function of the placenta were used: namely, dopplerometry of the uteroplacental-fetal complex.

To assess venous hemodynamics, we used ultrasound and Doppler methods of investigation. To assess the uterine-fetal-placental blood flow, the Doppler indices of the uterine artery blood flow rate (MA), umbilical cord artery (AP) and middle cerebral artery (Table 2) of the fetus (CMA) were recorded. Doppler study was included in the standard fetal ultrasound scan and was performed three times or more (depending on the indications) during pregnancy.

Studies of hemodynamic parameters in the terminal branches of the umbilical cord artery in pregnant women made it possible to determine an increase in vascular resistance only at 38–40 weeks of gestation ($P < 0.01$). A comprehensive analysis of these parameters showed that the earliest signs of an unfavorable course of pregnancy were changes in hemodynamics in the placenta during Doppler measurements with three-dimensional image reconstruction.

Despite careful pregravid preparation and observation during pregnancy, FPI was diagnosed in 5 (5.2%) patients: in 2 pregnant women with combined hypertensive disorders of moderate severity; in one patient of hypertensive disorders with a combination of grade II anemia, in 2 women with a burdened obstetric history (a history of more than 3 medical abortions, spontaneous abortions, missed pregnancies, repeated cases of antenatal fetal death). This dictates the need to allocate patients with repeated adverse pregnancy outcomes in history into a separate group of dispensary observation for in-depth diagnostic and therapeutic measures.

Table 2. Doppler indices of uteroplacental-fetal hemodynamics in women of the examined groups ($M \pm m$)

<i>Investigated parameter</i>	Main group n = 36	Comparison group n = 29
Systole-diastolic volume (LMS)		
<i>Uterine arteries</i>	2.18 ± 0.02 ***	1.89 ± 0.05
<i>Artery of the umbilical cord</i>	2.65 ± 0.05 ***	3.21 ± 0.02
<i>Middle cerebral artery</i>	4.65 ± 0.02 ***	2.82 ± 0.02
Resistance index (IR)		
<i>Uterine arteries</i>	0.39 ± 0.05 ***	0.61 ± 0.02
<i>Artery of the umbilical cord</i>	1.11 ± 0.02 ***	0.63 ± 0.01
<i>Middle cerebral artery</i>	0.74 ± 0.01 ***	0.91 ± 0.02
Ripple Index (PI)		
<i>Uterine arteries</i>	0.56 ± 0.02 ***	0.93 ± 0.05
<i>Artery of the umbilical cord</i>	0.65 ± 0.05 ***	0.84 ± 0.08
<i>Middle cerebral artery</i>	1.39 ± 0.02 ***	1.89 ± 0.02

Note * - differences relative to the data of the comparison group are significant (***) - $P < 0.001$)

Doppler analysis of various parts of the placenta in the 2nd and 3rd trimesters showed that the vascularization index in healthy pregnant women in the central zone is higher than in the paracentral and marginal regions (7.93 ± 0.08 ; 6.45 ± 0.06 ; 5.77 ± 0.06 respectively). This indicates that the central area of the placenta is the most functionally important site of the placenta.

Depending on the index of vascularization and the blood flow index in patients with reproductive losses, two variants of changes were revealed:

- in 42.3% of cases - a decrease in indices within placental hemodynamics by 1.5-2 times, which was regarded as hypovascularization of the placenta;
- in 57.7% of cases - an increase in the vascularization index by more than 1.5-2 times, which was interpreted as hypervascularization of the placenta.

The use of placental dopplerometry made it possible to detect minimal hemodynamic disturbances in the chorion and in the placenta.

The course of labor in patients with a history of reproductive loss was characterized by a rather high incidence of complications, which may be associated with an initial impairment of their reproductive function. In women in labor in the comparison group, significantly more often than in the main group, there was a violation of the regulation of labor in the form of an unsatisfactory labor process (21.9% and 9.3%) and weakness in labor (18.1% and 7.3%, respectively). In addition, in patients without pregravid preparation, acute fetal hypoxia during childbirth was 3.4 times more likely (10.5% and 3.1%, respectively). This led to a higher frequency of cesarean sections in the comparison group (21.9% and 11.5%, respectively).

Caesarean section in the groups was performed mainly in a planned manner (63.6% and 56.2%, respectively) according to the sum of relative indications. Of course, in patients with antenatal losses in the anamnesis, there was an expansion of indications for CS, taking into account the age of pregnant women, burdened by obstetric history, fetal condition. Attention is drawn to the fact that women in labor in the comparison group 2 times more often than in the main group experienced acute fetal hypoxia (2.6% and 1.05%, respectively).

It is obvious that the outcome of pregnancy is largely determined by the patient's pregravid state and the course of the entire gestational period. Studies have shown that in women of group I who underwent preliminary examination and treatment, in the vast majority of cases it was possible to identify and eliminate the main etiopathogenic factors causing antenatal losses. As a result, their pregnancy outcomes were significantly better than those of group II patients who did not seek medical help before the onset of a real pregnancy (Table 3).

The data presented in Table 3 are a convincing argument proving the necessity and obvious effectiveness of pregravid training for women with a history of reproductive losses. The overall incidence of adverse pregnancy outcomes (spontaneous abortions, missed pregnancies, antenatal fetal death, premature birth) in the study group was 2 times lower than in the comparison group (5.6% and 9.8%, respectively). It should be especially noted that there were no cases of antenatal fetal death in patients of the main group, and termination of pregnancy in the first and second trimesters was almost 2.5 times less frequent (2.8% and 6.8%, respectively).

Table 3. Pregnancy outcome in women surveyed groups

Pregnancy outcome	Main group (n = 36)		Comparison group (n = 29)	
	Abs.	%	Abs.	%
Urgent labor	34	94.5 *	23	79.3
Premature birth	2	5.6 *	3	10.3
Spontaneous miscarriage in the first trimester	-	-	one	3.4
Spontaneous miscarriage in the second trimester	one	2.8	one	3.4
Non-developing pregnancy	-	-	one	3.4
Antenatal fetal death	-	-	2	6.8

* Differences between the indicators of the compared groups are significant ($p < 0.05$).

Particularly significant is the fact that, despite the greater number of various complications during gestation, including FPI, antenatal losses in the prospective observation groups were minimal (6.8% in the comparison group), and most of the patients reported pregnancy before term of 37-40 weeks (the frequency of preterm birth was 5.6% and 10.3%, respectively).

CONCLUSION

Thus, pregnant women with reproductive loss of the fetus in a previous pregnancy constitute a group of extremely high perinatal risk of reproductive loss. Comprehensive pregravid examination of women with a history of reproductive loss of the fetus reveals risk factors for recurrent adverse outcomes of subsequent pregnancy: infectious, genetic, thrombophilic, hemodynamic, structural. This allows for treatment to reduce their pathological effects during implantation and placentation. Dynamic laboratory and instrumental examination, drug prevention of placental insufficiency from early pregnancy, development of individual obstetric tactics in pregnant women with a history of reproductive loss of the fetus are the key to improving perinatal outcomes and reducing perinatal morbidity.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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