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THE EFFECT OF IMPROVED METHODS OF MANAGEMENT OF WOMEN OF LATE REPRODUCTIVE AGE WITH ADENOMYOSIS IN THE FIRST HALF OF PREGNANCY ON THE DEVELOPMENT OF EARLY GESTATION COMPLICATIONS

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Summary

The prevalence of adenomyosis among endometriosis patients ranges from 20 to 70%. In recent years, several studies have reported a correlation between adenomyosis and major obstetric adverse outcomes. **The purpose of the study** is to reduce the number and severity of early gestational complications in women of late reproductive age with adenomyosis by developing and implementing scientifically based preventive and therapeutic methods of managing pregnant women in the first half of pregnancy. **Material and methods.** The influence of different methods of management of 89 women of late reproductive age with a previously radiologically established diagnosis of adenomyosis (group A) on the development of gestational complications in the first half of pregnancy was analyzed. Group A was randomized into two groups AI (n=45) with a developed management technique and AII (n=44) with traditional methods of management. Control group K consisted of 30 conditionally somatically and gynecologically

healthy pregnant women. **Results.** In pregnant women with adenomyosis, the placental processes have been violated, which in 7-8 weeks of gestation is manifested by a statistically significant decrease in the mean volume of chorion – (16.87 ± 0.24) cm^3 versus (17.58 ± 0.30) cm^3; an increase in the spiral arteries of the mean resistance index 1.18 times and the pulsation index 1.55 times; reduction of serum concentrations of progesterone 1.22 times, placental lactogen 1.21 times, β-human chorionic gonadotropin (β- HCG) - 1.37 times, free estriol - 1.28 times, protein A associated with pregnancy (PAPP-A) - 1.67 times, and endothelial dysfunction is manifested by a decrease in free L -arginine - 1,18 times and NO2- - 1,32 times. The application of the proposed pathogenetically sound prophylactic treatment of women with adenomyosis leads to a probable improvement of morphofunctional indicators of placentation and allows to reduce the number of complications in the first half of pregnancy, such as the threat of abortion by 2.56 times (OR 0.22; 95% CI 0.09-0.55), retrochorial hematomas - 2.13 times (OR 0.36; 95% CI 0.13-0.99), early miscarriages - 3.07 times (OR 0.26; 95% CI 0.08-0.88), late miscarriages - 2.05 times (OR 0.47; 95% CI 0.08-2.68), total miscarriages - 2.73 times (OR 0.27; 95% CI 0.09-0.77). **Conclusions.** Pregnancies in women with adenomyosis have an increased risk of numerous obstetric complications, especially early pregnancy loss, which requires more careful supervision of such women than previously thought, and requires the development of treatment and prevention methods of pregnancy management in the first half of pregnancy. Medical support during the early stages of pregnancy in pregnant women with adenomyosis according to the developed scheme led to a statistically significant decrease in complications in the first half of pregnancy.

Key words: adenomyosis, infertility, early gestational complications, miscarriage, retrochoric hematoma, risk of miscarriages, endothelial dysfunction, dopplerography, index of resistance, pulsation index, spiral and uterine arteries, dydrogesteron, L-arginine, obstetric complications, medical support.

Genital endometriosis has acquired the status of a "silent epidemic" and can safely be considered a disease of civilization. It affects every tenth woman of reproductive age, and the prevalence of adenomyosis among endometriosis patients ranges from 20 to 70% [7, 8, 15]. Adenomyosis is a benign condition defined as invasion of the endometrium into the myometrium with subsequent diffuse enlargement of the uterus, which histologically has ectopic endometrial glands and cytogenic stroma surrounded by hyperplastic and hypertrophic myometrium [5]. The modern definition of adenomyosis is a benign disease of the uterus, in which the invasion of endometrial glands and stroma into the myometrium occurs at a depth of more than 2.5 mm from the endometrial-myometrial junction with hyperplasia of smooth muscle tissue around [2, 12, 25, 31].

The medical and social significance of adenomyosis is caused not only by chronic pelvic pain and abnormal uterine bleeding, reduced work capacity, but also by the negative impact on the sexual and reproductive function of women [1, 6, 9, 16, 18]. Due to the difficulties of clinical and instrumental diagnosis and verification of adenomyosis, previously existing studies paid little attention to its influence on the course and outcomes of pregnancy. In recent years, several studies have reported a correlation between endometriosis and major obstetric adverse outcomes, such as miscarriage, premature rupture of membranes and premature birth, small-for-gestational-age fetus, gestational hypertension, preeclampsia, gestational diabetes, obstetric hemorrhage, placenta previa [4 , 8, 10, 13, 19, 23]. Other studies [3, 20] and a systematic review [17] did not fully confirm the increased risk of obstetric complications in patients with genital endometriosis. Therefore, it is necessary to study the direct influence of adenomyosis on the course of pregnancy, excluding the influence of the embryonic factor.

An important issue is to find out the pathogenetic mechanisms underlying gestational complications in adenomyosis. There are isolated data that explain the higher risk of obstetric

complications in women with endometriosis by the following factors: aberrant expression of some pro-inflammatory cytokines and prostaglandins, resistance of the endometrium to the selective action of progesterone, inflammation, impaired uterine contractility, excessive activation of the endometrium by free-radical metabolites, oxidative and nitrosative stress and the presence of anomalous invasion of the uterine connecting zone due to defective remodeling of the spiral arteries of the myometrium [14, 22, 24, 30]. A significant part of miscarriages in endometriosis, including adenomyosis, can be associated with immunological factors [11, 26].

Studying the features of the pathogenesis of implantation and gestational disorders in adenomyosis can contribute to the development of a pathogenetically based method of preconception preparation and preventive and therapeutic methods of pregnancy management in women with this pathology, which can lead to a decrease in gestational complications in the first half of pregnancy.

The purpose of the study is to reduce the number and severity of early gestational complications in women of late reproductive age with adenomyosis by developing and implementing scientifically based preventive and therapeutic methods of managing pregnant women in the first half of pregnancy.

Material and methods

The influence of different methods of management of 89 women of late reproductive age with a previously radiologically established diagnosis of adenomyosis (group A) on the development of gestational complications in the first half of pregnancy was analyzed. Group A was randomized into two groups AI and AII. The main AI group (n=45) included women who received dydrogesterone *per os* at 10 mg twice a day from the moment of pregnancy to 20 weeks of pregnancy; folic acid *per os* 5 mg once a day from the moment of pregnancy to 12 weeks of pregnancy; solution of L-arginine aspartate per os 5 ml four times a day from the 8th to the 10th and from the 14th to the 16th week of pregnancy.

When symptoms of threatened abortion appeared, women of group SI took 40 mg of dydrogesterone once *per os*, then 10 mg every 8 hours until the symptoms of threatened abortion disappeared, continued treatment in an effective dose for a week with further dose reduction (10 mg of dydrogesterone twice a day) until 20 weeks of gestation; suppositories rectally three times a day, one of which contained: Atropa bella-donna D2 – 1.1 mg, Calcium carbonicum Hahnemanni D8 – 4.4 mg, Matricaria recutita D1 – 1.1 mg, Plantago major D3 – 1.1 mg, Pulsatilla pratensis D2 - 2.2 mg, Solanum dulcamara D4 - 1.1 mg until symptoms of threatened abortion disappear; a solution of L-arginine aspartate per os 5 ml four times a day for two weeks; in the presence of bloody secretions from the genital tract or the development of a retrochorial hematoma, tranexamic acid was prescribed 500 mg four times a day for 4-5 days.

The AII comparison group (n=44) consisted of women who received folic acid 5 mg once a day from the moment of pregnancy to 12 weeks of pregnancy. When there was a threat of abortion, women were prescribed a homeopathic drug, one suppository of which contains: Atropa bella-donna D2 - 1.1 mg, Calcium carbonicum Hahnemanni D8 - 4.4 mg, Matricaria recutita D1 - 1.1 mg, Plantago major D3 - 1 ,1 mg, Pulsatilla pratensis D2 - 2.2 mg, Solanum dulcamara D4 - 1.1 mg, one rectal suppository three times a day; in the presence of bloody secretions from the genital tract or the development of a retrochorial hematoma, pregnant women received tranexamic acid 500 mg four times a day for 4-5 days.

Control group K consisted of 30 conditionally somatically and gynecologically healthy pregnant women.

During the instrumental examination of women, ultrasound with dopplerography was performed according to the standard method using ultrasound machines equipped with devices

with a pulsating wave doppler block and the function of color doppler capture and the possibility of further computer processing of dopplerograms. The echometric parameters of the uterus and ovaries, the growth and anatomy of the fetus, the thickness and volume of the chorion/placenta at 7-8, 11-12 and 18 weeks of pregnancy were evaluated, the resistance index (IR) and pulsatile index (PI) of blood flow in the spiral and uterine arteries were determined arteries, intrauterine state of the fetus.

To assess the function of the corpus luteum of pregnancy, the chorion and the placenta, peripheral blood hormones such as placental lactogen were determined by the solid-phase enzyme-linked immunosorbent assay using an ELISA analyzer and test systems, IBL (Germany); β-hCG and progesterone - using an immunochemical method with electrochemiluminescence detection using an analyzer and test systems Cobas 6000, Roche Diagnostics (Switzerland); free estriol and PAPP-A - immunochemical method with chemiluminescent detection using Immulite analyzer and test systems.

The concentration of total nitrite anions (NO2-) was determined using the reaction with the Gryss-Ilosvay reagent. Quantification of nitrite anions (NO2-) is based on spectrophotometry of the dye formed in the visible and ultraviolet part of the spectrum, since the azo dye formed has an optical density proportional to the concentration of nitrite anions. Extinction was recorded at a wavelength of 540 nm.

The content of free L-arginine in blood serum was determined by the classical Sakaguchi method, which is based on the mechanism of formation of a stable-colored complex of orange-red arginine with α-naphthol in the presence of an oxidant. The amount of arginine was calculated according to the calibration schedule drawn up in accordance with the conditions of the experiment and which is a curve of dependence of the optical density on the amount of arginine.

Sample data were assessed using quantitative, nominal and ranked scales. The obtained results were processed on an IVM PC using the Excel program package and methods of analytical statistics: using the sampling method, the parameters of the general population were estimated based on the sample data; statistical criteria were used to determine the validity of the proposed hypotheses: the t-test was used to compare the average values of independent samples and connected (dependent) samples; χ^2-criterion – for analyzing the conjugation of features, comparing event frequencies; correlation analysis - to study stochastic dependence between indicators; odds ratio (OR) – to estimate the ratio of the odds of an event in the compared groups; A 95% confidence interval (CI) is an interval within which the magnitude of the effect may vary. A value of VS from zero to one corresponded to a decrease in risk, greater than one to its increase, and equal to one to the absence of an effect.

Results and their discussion

The average age of pregnant women with adenomyosis of group A was (38.62 ± 0.39) years, group AI – (37.49 ± 0.65) years, AII – (37.75 ± 0.52) years, K – (37.81 ± 0.65) years, p>0.05.

The term of registration of pregnant women in the women's consultation in group A was (6.65 ± 0.07) weeks of pregnancy, in group AI – (6.60 ± 0.09) weeks, in group AII – (6.70 ± 0.12) weeks, in group K – (6.63 ± 0.09) weeks and did not differ significantly between groups.

When consulting a doctor, 68.54% (61) of pregnant women with adenomyosis complained of pain in the lower abdomen or lower back, of which 31 (68.89%) pregnant women in group AI and 30 (68.18%) pregnant women in group AII (p>0.05). Pulling (46.07% (41)) and periodic (48.31% (43)) nature of pain prevailed. Less often, pregnant women of group A were bothered by pain during physical exertion (39.33% (35)), spasmodic (19.10 % (17)) and constant pain (17.98% (16)). In groups AI and AII, the nature of pain in the lower abdomen and lower back at 6-7 weeks of pregnancy had no significant differences. 29.21% (26) of pregnant women in group A at the first

visit to the doctor, they had complaints of bleeding from the genital tract, of which 31.11% (14) in the AI group and 27.27 (12) in the AII group (p>0.05).

Thoroughly studied gynecological anamnesis of pregnant women. When analyzing the nature of menstrual function, it was established that the age of menarche in group A was 1.07 times greater than that in group K (p<0.01), the number of menstrual cycles per year was 1.10 times less (p<0, 01), the duration of menstruation is 1.15 times longer (p<0.02) and the menstrual cycle is 1.29 times longer (p<0.02) (Table 1).

Table 1 – Character of menstrual function in examined women before pregnancy

Group	Age at menarche, M ± SE, in years	The number of MCs for a year, n (%)	Duration of menstruation, M ± SE, in days	MC duration, M ± SE, in days
A, n=89	13.38 ± 0.09 [k]	11.84 ± 0.27 [k]	5.81 ± 0.13 [k]	35.99 ± 2.96 [k]
AI, n=45	13.42 ± 0.14 [k]	11.82 ± 0.43 [k]	5.69 ± 0.29 [k]	37.47 ± 4.76 [k]
AII, n=44	13.35 ± 0.13 [k]	11.86 ± 0.35 [k]	5.93 ± 0.15 [k]	34.48 ± 3.52 [k]
K, n=30	12.47 ± 0.22	13.08 ± 0.09	5.03 ± 0.14	27.93 ± 0.17
Notes: 1. [k] is a statistically significant difference with the indicators of the group K, p<0.05; 2. No statistically significant difference between AI and AII indicators was found, p>0.05.				

Groups AI and AII were homogeneous in age of menarche, number of MCs per year, duration of menstruation and MCs.

When comparing the nature of menstruation in pregnant women with adenomyosis compared to controls, it was found that the groups were homogeneous in terms of the distribution of regular and irregular menstruation, but in group A the number of women with painful menstruation was 1.72 times greater (62.92% (56) versus 36 .67% (11), p<0.02) and with abundant - by 2.70 times (44.94% (40) vs. 16.67% (5), p<0.01), while in the group K there were more people with painless menstruation by 1.71 times (68.33% (19) vs. 37.08% (33), p<0.02) and with moderate ones by 1.55 times (83.33% (25) against 53.93% (48), p<0.01). Groups AI and AII were homogeneous in the distribution of regular, irregular, painful, scanty, moderate and abundant menstruation (Table 2).

Table 2 – Pattern of menstruation in examined women before pregnancy, n (%)

Group	Regular	Irregular	Painful	Scarce	Moderate	Abundant
A, n=89	83(93.26)	6(6.74)	56(62.92) [к]	1(1.12)	48(53.93) [к]	40(44.94) [к]
AI, n=45	41(91.11)	4(8.89)	27(60.00) [k]	1(2.22)	25(55.56) [k]	19(42.22) [k]
AII, n=44	42(95.45)	2(4.55)	29(65.91) [k]	0(0.00)	23(52.27) [k]	21(47.73) [k]
K, n=30	30(100)	0(0.00)	11(36.67)	1(3.33)	25(83.33)	5(16.67)
Notes: 1. [k] is a statistically significant difference with the indicators of the group K, p<0.05; 2. No statistically significant difference between AI and AII indicators was found, p>0.05.						

The average age of the beginning of sexual life in group A ((18.89 ± 0.21) years), in group AI ((18.76 ± 0.28) years), in group AII ((19.02 ± 0.32) years) and group K ((18.00 ± 0.29) years) had no statistically significant differences.

Among gynecological diseases in the anamnesis, ectopy of the cylindrical epithelium of the cervix was observed in 22.47% (20) of women in group A and 26.67% (8) in group K (p>0.05). There were no operative interventions on the organs of the abdominal cavity in the studied patients.

17.98% (16) of pregnant women with adenomyosis and 13.33% (4) women of the control group had urogenital infections and/or vaginal dysbiosis in the anamnesis. Violation of the urogenital microbiota was most often manifested in all groups by bacterial vaginosis, which was noted in every eighth to ninth woman.

When studying reproductive anamnesis, it was found that 49.44% (44) of women of group A had previously been pregnant, including 55.56% (25) of group AI, 43.18% (19) of group AII, and in group CI – 40.00% (18). The average number of previous pregnancies, respectively, was (0.94 ± 0.12); (1.00 ± 0.16); (0.89 ± 0.19) and (1.10 ± 0.20), p>0.05. The studied groups A, AI, AII and KI were homogeneous not only in the frequency of presence in the anamnesis and the average number of pregnancies, but also in births (Table 3).

Table 3 – Reproductive history of examined women

Group	Number of women with a history of pregnancy,n (%)	Average number pregnancies, M ± SE	The number of women with a history of childbirth, n (%)	Average number of births, M± SE	The number of women with a history of artificial abortions, n (%)	Average amount artificial abortions, M±SE
A, n=89	44(49.44)	0.94 ± 0.12	27(30.34)	0.37 ± 0.06	16(17.98) [k]	0.20 ± 0.05 [k]
AI, n=45	25(55.56)	1.00 ± 0.16	15(33.33)	0.40 ± 0.09	9(20.00) [k]	0.22 ± 0.07 [k]
AII, n=44	19(43.18)	0.89 ± 0.19	12(27.27)	0.34 ± 0.07	7(15.91) [k]	0.18 ± 0.07 [k]
K, n=30	18(40.00)	1.10 ± 0.20	9(30.00)	0.37 ± 0.11	13(43.33)	0.70 ± 0.17
Notes: 1. [k] is a statistically significant difference with the indicators of the group K, p<0.05; 2. No statistically significant difference between AI and AII indicators was found, p>0.05.						

Every third of the examined women with adenomyosis and controls had a history of giving birth. The average number of births per woman was equal in group A (0.37 ± 0.06) and in group K – (0.37 ± 0.11). Among women with adenomyosis, pregnancies ended in artificial abortion 2.41 times less often (17.98% (16) versus 43.33% (13), p<0.01), respectively, the average number of artificial abortions per woman was 3 times less .50 times ((0.20 ± 0.05) vs. (0.70 ± 0.17), p<0.01).

A characteristic feature of the reproductive history of women with adenomyosis was a 7.42 times higher frequency of miscarriages (24.72% (22) vs. 3.33% (1), p<0.01) and an average number of miscarriages per woman of 12.33 times (0.37 ± 0.08 vs. 0.03 ± 0.03, p<0.01). The frequency (26.67 % (12) vs. 22.73 % (10)) and the average number of miscarriages (0.38 ± 0.11 vs. 0.36 ± 0.11) between the AI and AII groups did not have significant differences

The study of somatic anamnesis showed that 29.21% (26) of patients of group A had extragenital diseases (p<0.01). Pathology of the cardiovascular system was registered in 10.11% (9) of women of group C (p>0.05), the respiratory system – in 3.37% (3) (p>0.05), the gastrointestinal tract – in 15.73% (14) (p<0.03), biliary system – in 8.99% (10) (p>0.05), urinary system – in 7.87% (7) (p>0, 05). The distribution of somatic diseases in groups with adenomyosis had no statistically significant differences.

Therefore, the studied groups AI and AII were homogeneous in terms of symptoms of the threat of miscarriage (pain in the lower abdomen and lower back, bleeding from the genital tract), average age, age of menarche, number of MCs per year, nature of menstrual function, age of onset of sexual life, frequency and the distribution of urogenital infections and gynecological morbidity, the nature of the reproductive anamnesis, the presence and distribution of somatic pathology, the term of enrollment, which made it possible to compare further research results.

In the pregnant studied groups, in addition to complex ultrasound, we used the three-dimensional reconstruction module to study the volume of the chorion and the ADF function - indicators of the uterine (pre-) placental blood flow that is forming and the blood flow in the uterine vessels.

As can be seen from the table. 4, the volume of the chorion in pregnant women with adenomyosis was smaller than that in control pregnant women - (16.87 ± 0.24) cm^3 versus (17.58 ± 0.30) cm^3.

Table 4 – Sonographic and Doppler markers of placentation in pregnant women at 7-8 weeks of gestation

Group	The volume of the chorion, cm^3	Average rate of blood flow in spiral arteries		The average rate of blood flow in the uterine arteries	
		IR	PI	IR	PI
A, n=89	16.87 ± 0.24 [k]	0.66 ± 0.01 [k]	1.33 ± 0.02 [k]	0.88 ± 0.01	1.84 ± 0.02 [k]
AI, n=45	16.83 ± 0.30 [k]	0.66 ± 0.01 [k]	1.33 ± 0.02 [k]	0.88 ± 0.01	1.83 ± 0.02 [k]
AII, n=44	16.91 ± 0.39 [k]	0.67 ± 0.01 [k]	1.34 ± 0.03 [k]	0.89 ± 0.02	1.85 ± 0.03 [k]
K, n=30	17.58 ± 0.30	0.56 ± 0.01	0.86 ± 0.02	0.87 ± 0.01	1.74 ± 0.02
Notes: 1. [k] is a statistically significant difference with the indicators of the group K, $p<0.05$; 2. No statistically significant difference between AI and AII indicators was found, $p>0.05$.					

Defective deep placentation in group A at 7-8 weeks of pregnancy was manifested by an increase in the spiral arteries of the average IR by 1.18 and PI by 1.55 times ((0.66 ± 0.01) versus (0.56 ± 0.01) ($p<0.01$) and (1.33 ± 0.02) vs. (0.86 ± 0.02) ($p<0.01$)) and the average PI in uterine arteries - 1.06 times ((1.84 ± 0.02) versus (1.74 ± 0.02) ($p<0.01$)).

The profile of hormones involved in the development and maintenance of pregnancy was characterized in pregnant women with adenomyosis at 7-8 weeks of gestation by a decrease in serum concentrations of progesterone by 1.22 times ((21.52 ± 0.57) ng/ml against (26.28 ± 0.55) ng/ml), placental lactogen – 1.21 times ((0.151 ± 0.003) mg/l versus (0.182 ± 0.009) mg/l), hCG – 1.37 times ((81.50 ± 2.68) ng/ml versus (112.07 ± 9.24) ng/ml), estriol – 1.28 times ((1.49 ± 0.04) nmol/l versus (1.90 ± 0 .09) nmol/l), PAPP-A – 1.67 times ((0.29 ± 0.01) mIU/l vs. (0.48 ± 0.05) mIU/l) (Fig. 1).

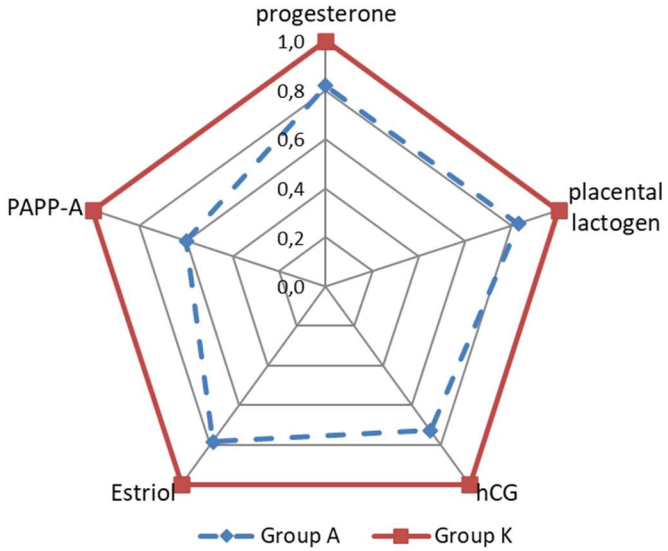

Figure 1 – Shift relative to reference indicators of hormones involved in placentation in pregnant women with adenomyosis at 7-8 weeks of gestation.

The nitrosative status of pregnant women with adenomyosis was distinguished by a 1.18-fold reduced level of free L-arginine ((29.63 ± 0.44) vs. (34.96 ± 0.40) mg/l) and a 1.32-fold decrease in NO2- ((20.15 ± 0.32) versus (26.51 ± 0.30) μmol/l).

Groups AI and AII were homogeneous according to all studied sonographic, dopplerographic and biochemical markers of placentation at 7-8 weeks of pregnancy.

Therefore, for pregnant women with adenomyosis at 7-8 weeks of gestation, there was a statistically significant decrease in the average volume of the chorion; increase in the spiral arteries of the average IR and PI and the average PI in the uterine arteries; decrease in serum concentrations of progesterone, placental lactogen, β-hCG, estriol, PAPP-A, free L-arginine and nitrite anions (NO2-).

When pregnant women with adenomyosis were observed, early miscarriages occurred before the 12th week of pregnancy in 4 pregnant women of the AI group and in 12 women of the AII group, and late miscarriages occurred in 2 and 4 women, respectively. Therefore, a comparative assessment of the investigated sonographic, dopplerographic and biochemical indicators at 12 weeks of pregnancy was carried out between 41 pregnant women of the AI group and 32 pregnant women of the AII group and at 18 weeks between 39 pregnant women of the AI group and 28 pregnant women of the AII group.

The analysis of the study of the dynamics of the presence of pain syndrome showed a statistically significantly greater effectiveness of the management of pregnant women with adenomyosis according to the developed scheme. Pain syndrome at 12 weeks of gestation was noted in pregnant women of the AI group 2.67 times less often than in the AII group - 25.00% (10) versus 66.67% (20) (OR 0.17; 95% CI 0.06 -0.47; p<0.01); at 18 weeks in 3.78 – 15.00% (8) versus 56.67% (17) (OR 0.14; 95% CI 0.04-0.42; p<0.01) (see fig. 2). The specific gravity of all types of pain at 12 and 18 weeks of gestation in the AI group was statistically significantly lower than the similar one in the AII group: pulling – by 2.22 and 3.47 times; striated - by 13.33% and 10.00%; constant - 6.67 and 8.00 times; during physical exertion - in 4.67 and 5.33; periodic - 4.00 times.

Analysis of the dynamics of chorionic and placental volumometry indicators according to ultrasound data in women with adenomyosis, depending on medical support in the early stages of pregnancy, revealed a statistically significant decrease in the volume of the placenta compared to control indicators at 12 and 18 weeks of gestation in the AI group by 1.08 times and by 1.14

times ((83.82 ± 1.53) cm^3 and (178.53 ± 3.27) cm^3) and in group AII – by 1.51 times and by 1.74 times ((60.15 ± 1.48) cm^3 and (117.04 ± 3.01) cm^3) ((90.72 ± 1.82) cm^3 and (204.12 ± 4.09) cm^3) ($p<0.01$).

As can be seen from fig. 2, fig. 3, the volume of the placenta in pregnant women with adenomyosis who received the proposed medical support exceeded the corresponding indicator in the group of women with traditional at 12 weeks by 1.39 times ($p<0.01$), and at 18 weeks by 1.53 ($p<0.01$).

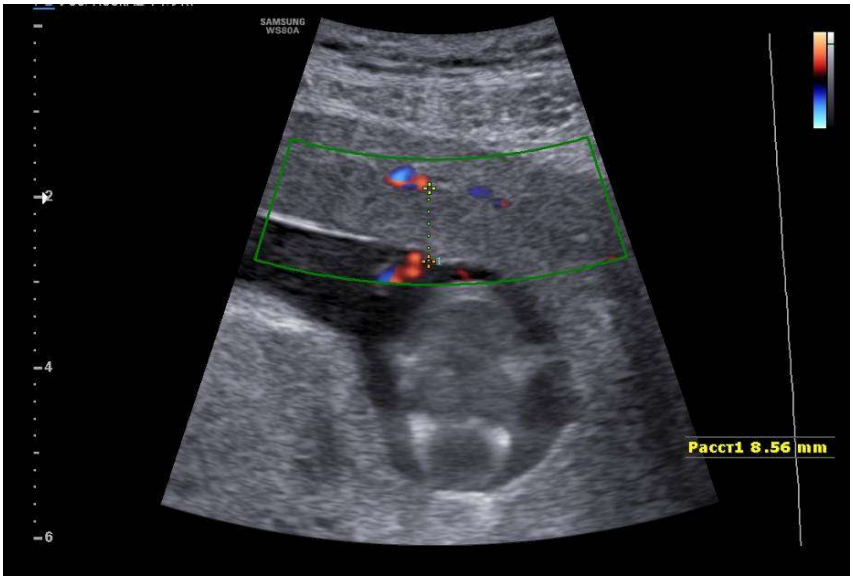

Figure 2 – Color dopplerography. Thinning of the placenta and reduction of its volume in a woman with adenomyosis group AII with traditional methods of pregnancy management at 12 weeks of gestation.

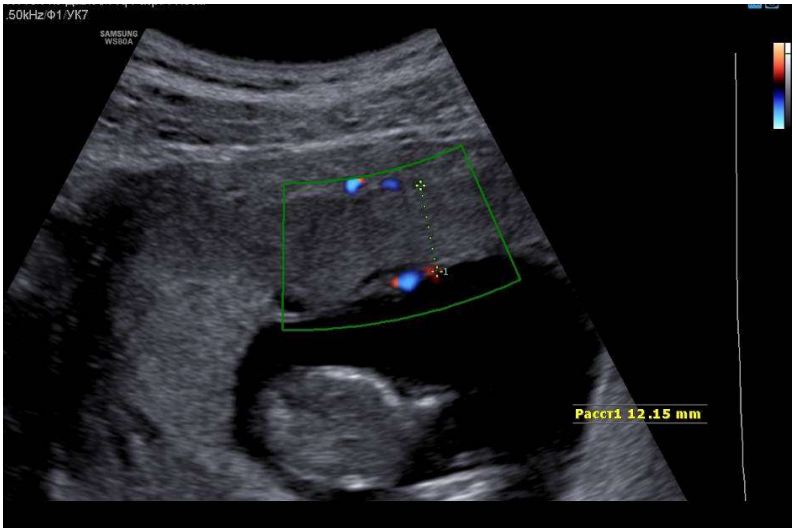

Figure 3 – Normal thickness and volume of the placenta in a woman with AI group adenomyosis with the developed method of pregnancy management at 12 weeks of gestation.

Analysis of dopplerographic markers of placentation in pregnant women with adenomyosis in the dynamics of the first half of pregnancy showed the advantages of using the developed method of managing the early gestational period in adenomyosis (Fig. 4, Fig. 5).

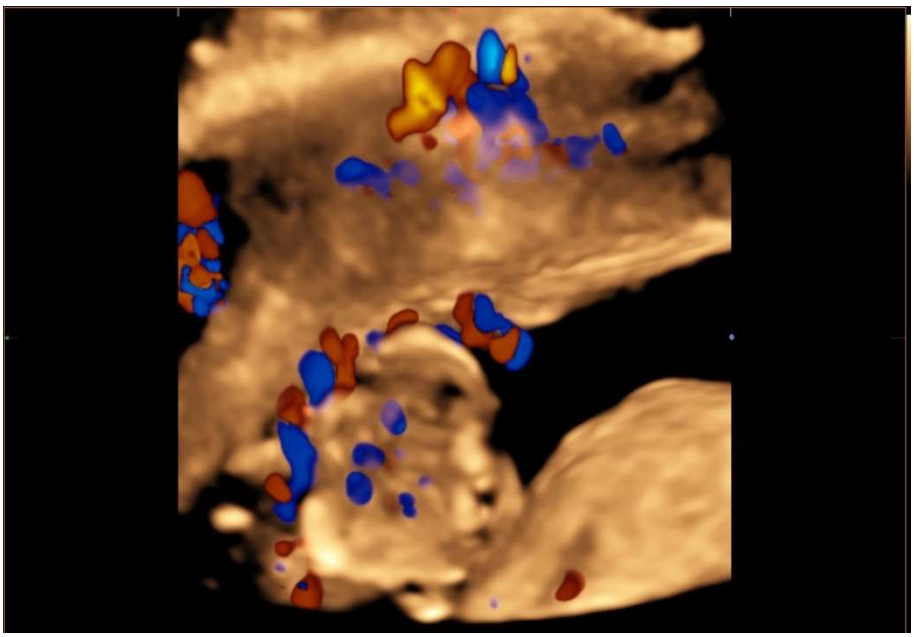

Figure 4 – Color dopplerography. Insufficiency of remodeling of spiral arteries, which is compensated by increased blood flow resistance in pregnant group AII.

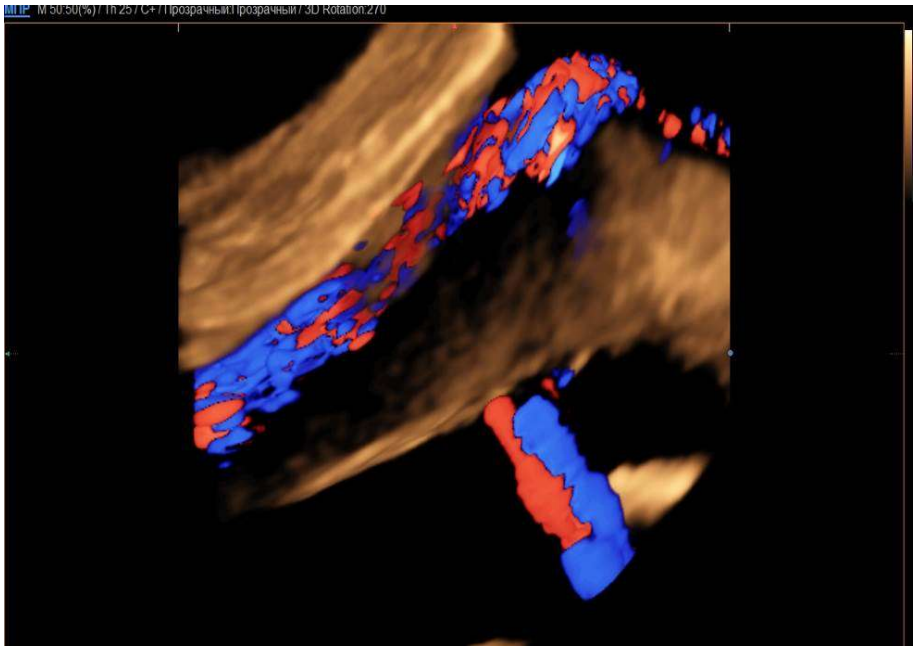

Figure 5 – Color dopplerography. Complete remodeling of spiral arteries with normal indicators of blood flow resistance in the AI pregnant group.

As can be seen from fig. 6, in the AI group, IR in spiral arteries at 11-12 weeks of pregnancy was 1.08 times lower than that in the AII group ((0.56 ± 0.01) versus (0.61 ± 0.01), p< 0.02); at 18 weeks – by 1.10 ((0.44 ± 0.01) vs. (0.48 ± 0.01), p<0.01), and in the uterine arteries – by 1.04 times ((0 .79 ± 0.02) vs. (0.82 ± 0.01), p>0.05) and in 1.13 ((0.59 ± 0.02) vs. (0.67 ± 0.01), p<0.01). The PI was lower in the AI group than in the AII group in spiral arteries at 11-12 weeks of pregnancy by 1.08 times ((0.85 ± 0.01) versus (0.92 ± 0.01), p<0 ,01); at 18 weeks – by 1.07 ((0.66 ± 0.01) versus (0.71 ± 0.01), p<0.04), and in the uterine arteries – by 1.19 times, respectively ((2 .49 ± 0.03) vs. (2.97 ± 0.01), p>0.04) and in 1.51 ((1.73 ± 0.06) vs. (2.62 ± 0.04), p<0.01).

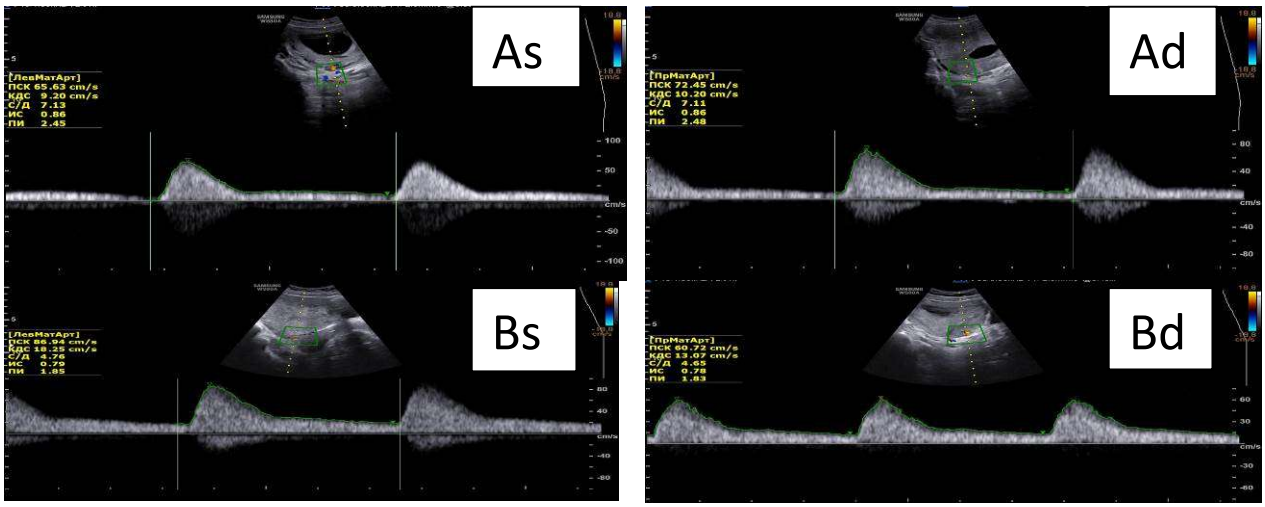

Figure 6 - Color and spectral dopplerography: A - in pregnant Z. group AII with traditional management at 11 weeks and 4 days: As - increased PI of blood flow in the left (2.45) uterine artery, Ad - in the right (2.48) ; B – in pregnant Sh. of group AI at 11 weeks and 5 days with the management of the correspondingly developed methodology: Bs – corresponding to the physiological norm of PI blood flow in the left uterine artery (1.85); Bd is the PI of blood flow in the right uterine artery (1.83).

A study of the levels and displacement of biochemical markers of placentation in pregnant women with adenomyosis relative to controls in the dynamics of the first half of pregnancy, depending on medical support, was conducted (Table 5).

Table 5 – Levels of biochemical markers of placentation in pregnant women with adenomyosis depending on medical support, M ± SE

Indicator	Research term	Group AI	Group AII	Group K
PAPP-A, mU/ml	7-8 weeks	0.31 ± 0.01 ^{k}	0.26 ± 0.01 ^{k}	0.48 ± 0.05
	11-12 weeks	2.31 ± 0.02 ^{k,all}	2.02 ± 0.04 ^{k,al}	2.66 ± 0.09
	18 weeks	7.78 ± 0.31 ^{all}	6.55 ± 0.40 ^{k,al}	8.29 ± 0.28
Estriol, ng/ml	7-8 weeks	1.51 ± 0.05 ^{k}	1.48 ± 0.07 ^{k}	1.90 ± 0.09
	11-12 weeks	6.18 ± 0.24 ^{k,all}	5.43 ± 0.35 ^{k,al}	6.63 ± 0.24
	18 weeks	14.82 ± 0.58 ^{all}	12.74 ± 0.38 ^{k,al}	15.47 ± 0.53
β- HCG, ng/ml	7-8 weeks	79.63 ± 3.55 ^{k}	83.42 ± 4.03 ^{k}	112.07 ± 9.24
	11-12 weeks	32.02 ± 2.30 $^{.all}$	27.29 ± 1.39 ^{k,al}	36.17 ± 2.26
	18 weeks	6.92 ± 0.42 ^{k,all}	4.61 ± 0.34 ^{k,al}	8.87 ± 0.51
Placental lactogen, mg/l	7-8 weeks	0.155 ± 0.005 ^{k}	0.146 ± 0.009 ^{k}	0.182 ± 0.009
	11-12 weeks	0.656 ± 0.009 ^{k,all}	0.586 ± 0.008 ^{k,al}	0.728 ± 0.013
	18 weeks	2.715 ± 0.052 ^{k,all}	1.670 ± 0.090 ^{k,al}	2.987 ± 0.078
Progesterone, ng/ml	7-8 weeks	21.32 ± 0.79 ^{k}	21.71 ± 0.84 ^{k}	26.28 ± 0.55
	11-12 weeks	32.43 ± 0.51 ^{k,all}	30.30 ± 0.88 ^{k,al}	35.92 ± 0.39
	18 weeks	42,95 ± 0,77 ^{all}	37.90 ± 0,81 ^{k,all}	43.13 ± 0,20
Note. $^{k, al, all}$ – statistically significant difference with the indicators of groups K, AI, AII (p<0,05).				

As can be seen from the table. 5, the management of pregnant women according to the developed methodology led to the normalization of such indicators as PAPP-A, estriol, progesterone in the AI group at 18 weeks of pregnancy, while none of the studied markers of placentation normalized in the AII group.

The effectiveness of the developed method of managing pregnant women with adenomyosis was demonstrated by the fact that serum levels of progesterone in the AI group at 11-12 weeks of pregnancy were statistically significantly higher compared to those in the AII group by 1.07 times ((32.43 ± 0.61) ng/ ml vs. (30.30 ± 0.88) ng/ml) and at 18 weeks – 1.13 times ((42.95 ± 0.77) ng/ml vs. (37.90 ± 0.81) ng/ ml); placental lactogen - 1.12 times ((0.66 ± 0.01) mg/l versus (0.59 ± 0.01) mg/l) and 1.63 times ((2.71 ± 0.05) mg/l versus (1.67 ± 0.09) mg/l); β-HCl - 1.17 times ((32.02 ± 2.30) ng/ml vs. (27.29 ± 1.39) ng/ml) and 1.50 times ((6.92 ± 0, 42) ng/ml versus (4.61 ± 0.34) ng/ml); free estriol - 1.14 times ((6.18 ± 0.24) ng/ml vs. (5.43 ± 0.35) ng/ml) and 1.16 times ((14.82 ± 0.58) ng/ml versus (12.74 ± 0.38) ng/ml); PAPP-A - 1.14 times ((2.31 ± 0.02) mU/ml vs. (2.02 ± 0.04) mU/ml) and 1.19 times ((7.78 ± 0, 31) mU/ml versus (6.55 ± 0.40) mU/ml).

The application of the developed method of managing pregnant women in the AI group led at 18 weeks of pregnancy to the normalization of the studied indicators of nitrosative homeostasis, such as free L-arginine and nitrite anions (NO2-). Indicators of nitrosative homeostasis during traditional management of pregnant women with adenomyosis were statistically significantly different from those in controls throughout the first half of pregnancy. At 11-12 weeks of gestation, the levels of L-arginine in the AI group exceeded those in the AII group by 1.07 times ((34.14 ± 0.55) mg/l vs. (31.88 ± 0.71) mg/l , p<0.03) and within 18 weeks – 1.18 times ((46.91 ± 0.36) mg/l vs. (41.17 ± 0.37) mg/l, p<0.01); and nitrite anions (NO2-) – 1.07 times ((24.38 ± 0.63) nmol/l vs. (22.86 ± 0.54) nmol/l, p<0.01) and in 1 .19 times ((29.72 ± 0.44) nmol/l vs. (28.62 ± 0.30) nmol/l, p<0.01) (Table 6).

Table 6 – Nitrosative status of peripheral blood in pregnant women with adenomyosis depending on medical support, M ± SE

Indicator	Research term	Group AI	Group AII	Group K
Free L-arginine, mg/l	7-8 weeks	29.01 ± 0.55 ^{kl}	30.26 ± 0.70 ^{kl}	34.96 ± 0.40
	11-12 weeks	34.14 ± 0.55 ^{kl,all}	31.88 ± 0.71 ^{kl,al}	38.35 ± 0.40
	18 weeks	46.91 ± 0.36 ^{all}	41.17 ± 0.37 ^{kl,al}	47.85 ± 0.37
NO2-, nmol/l	7-8 weeks	20.34 ± 0.49 ^{kl}	19.97 ± 0.39 ^{kl}	28.72 ± 0.44
	11-12 weeks	24.38 ± 0.63 ^{kl,all}	22.86 ± 0.54 ^{kl,al}	24.16 ± 0.68
	18 weeks	29.72 ± 0.44 ^{all}	28.62 ± 0.30 ^{kl,al}	29.43 ± 0.25
Note. $^{k, al, all}$ – statistically significant difference with the indicators of groups K, AI, AII (p<0.05).				

The use of the developed method of pregnancy management in women with adenomyosis led to a statistically significant decrease in complications in the first half of pregnancy: the threat of termination of pregnancy by 2.56 times (22.22% (10) versus 56.82% (25), p<0.01 ; VS 0.22; 95% CI 0.09-0.55), the number of cases of retrochorial hematoma - 2.13 times (15.55% (7) vs. 34.09% (15), p<0.04 ; SD 0.36; 95% CI 0.13-0.99), early miscarriages - 3.07 times (8.89% (4) vs. 27.27 (12), p<0.02; SD 0 .26; 95% CI 0.08-0.88), late miscarriages – 2.05 times (4.44 (2) vs. 9.09 (4), p>0.05; VS 0.47; 95 % CI 0.08-2.68), of all miscarriages - 2.73 times (13.39 % (6) vs. 36.36 % (16), p<0.01; SD 0.27; 95% CI 0.09-0.77) (Table 7).

Table 7 – Early complications of pregnancy in examined women, n (%)

Indicator	Group AI	Group AII	Group K
Threat of abortion	10(22.22) ^{kl,all}	25(56.82) ^{kl,al}	1(3.33)
Retrochorial hematoma	7(15.55) ^{kl,all}	15(34.09) ^{kl,al}	0(0.00)
Early toxicosis of pregnancy	3(6.67)	4(9.09)	1(3.33)
Early miscarriage	4(8.89) ^{kl,all}	12(27.27) ^{kl,al}	0(0.00)
Late miscarriage	2(4.44)	4(9.09)	0(0.00)
Total miscarriages	6(13.39) ^{kl,all}	16(36.36) ^{kl,al}	0(0.00)
Iron deficiency anemia	16(35.56)	19(43.18)	7(23.33)
Note: $^{k, al, all}$ – statistically significant difference with the indicators of groups K, AI, AII ($p<0.05$).			

Conclusions

Genital endometriosis occurs in 10-15% of women of reproductive age, of which adenomyosis is registered in 20-70% of cases. Pregnancies in women with adenomyosis have an increased risk of numerous obstetric complications, especially early pregnancy loss, which requires more careful supervision of such women than previously thought, and requires the development of treatment and prevention methods of pregnancy management in the first half of pregnancy.

Medical support during the early stages of pregnancy in pregnant women with adenomyosis according to the developed scheme led to a statistically significant decrease in complications in the first half of pregnancy: the threat of termination of pregnancy by 2.56 times (OR 0.22; 95% CI 0.09-0.55) , the number of cases of retrochorial hematoma – 2.13 times (OR 0.36; 95% CI 0.13-0.99), early miscarriages – 3.07 times (OR 0.26; 95% CI 0.08-0.88), late miscarriages – 2.05 times (OR 0.47; 95% CI 0.08-2.68), total miscarriages – 2.73 times (OR 0.27; 95% CI 0, 09-0.77).

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