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EVALUATION OF THE EFFECT OF DIFFERENT METHODS OF CURACY ON WOMEN WITH ADENOMYOSIS IN THE FIRST HALF OF PREGNANCY ON THE DEVELOPMENT OF EARLY GESTATIVE COMPLICATIONS

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Abstract

Pregnancy in women with adenomyosis has an increased risk of multiple obstetric complications, especially early pregnancy losses. **The purpose of the study** was to conduct a comparative analysis of the impact of different methods of curation of pregnant women on the development of early gestational complications. **Material and methods.** There were 89 pregnant women with a pre-radiologically diagnosed adenomyosis. The main group (n = 45) included women receiving 10 mg twice daily hydrochloride *per os* from the time of pregnancy to 20 weeks of gestation; folic acid *per os* at 400 mcg once a day from the moment of establishment of pregnancy to 12 weeks of pregnancy; solution of L-arginine aspartate *per os* 5 ml four times daily from 8th to 10th and from 14th to 16th week of pregnancy. The comparison group (n = 44) was comprised of women receiving folic acid 400 µg once daily from the time of pregnancy until 12 weeks of gestation. In the instrumental examination of women, ultrasound was performed with Doppler. To evaluate the function of the yellow body of pregnancy, chorion and placenta it were determined such hormones of peripheral blood as placental lactogen, human β-chorionic gonadotropin, progesterone, free estriol and PAPP-A. Serum concentrations of total nitrite anions (NO₂⁻) and free L-arginine were studied in serum. Early pregnancy complications were assessed. **Results.** Carrying out medical support for

early gestation in pregnant women with adenomyosis according to the developed scheme has led to a decrease in the number of presence of pain syndrome in 12 weeks of gestation by 2.67 times (OR 0.17; 95% CI 0.06-0.47; $p < 0.01$); at 18 weeks - at 3.78 (OR 0.14; 95% CI 0.04-0.42; $p < 0.01$); decrease in placenta volume by 1.39 times ($p < 0.01$) and 1.53 ($p < 0.01$); IP in spiral arteries 1.08 times ($p < 0.01$) and 1.07 ($p < 0.04$), and in uterine arteries respectively 1.19 times ($p > 0.04$) and 1.51 ($p < 0.01$); increase in serum progesterone levels 1.07 times ($p < 0.01$) and 1.13 ($p < 0.01$); placental lactogen - by 1.12 ($p < 0.01$) and in 1.63 ($p < 0.01$); β -HCG at 1.17 ($p < 0.01$) and 1.50 ($p < 0.01$); free estriol - by 1.14 ($p < 0.01$) and 1.16 ($p < 0.01$); PAPP-A - 1.14 ($p < 0.01$) and 1.19 ($p < 0.04$), free L-arginine - 1.07 times ($p < 0.03$) and 1.18 ($p < 0.01$); nitrite anions (NO_2^-) - by 1.07 ($p < 0.01$) and 1.19 ($p < 0.01$). The use of the proposed method of pregnancy management in women with adenomyosis led to a statistically significant reduction in complications in the first half of pregnancy: the risk 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 (OR 0.36; 95% CI 0.13-0.99), early miscarriages - 3.07 (OR 0.26; 95% CI 0.08-0.88), late miscarriages - by 2.05 (OR 0.47; 95% CI 0.08-2.68), total miscarriages - 2.73 (OR 0.27; 95% CI 0.09-0.77).

Conclusions. Patients with adenomyosis are at high risk for early gestational complications, such as the risk of termination of pregnancy, retrochorial hematomas and miscarriages. Preventive treatment support for such pregnant women should include, along with folic acid preparations, dydrogesterone preparations from the time of pregnancy up to 20 weeks, a solution of L-arginine aspartate *per os* for 2 weeks during periods of deep placentation.

Key words: adenomyosis; ultrasound; Doppler; spiral arteries; chorion; placenta; placental lactogen; human chorionic gonadotropin; PAPP-A; progesterone; free estriol; nitrites; free L-arginine; early gestational complications.

Genital endometriosis occurs in 10-15% of women of reproductive age, of whom in 20-70% of cases adenomyosis is registered [2, 5, 11]. Diagnosis of adenomyosis presents some difficulties, but the use of modern instrumental diagnostic technologies has made it possible to detect this disease with high specificity and diagnostic sensitivity [3, 4, 6-8, 12-14]. Pregnancies in women with adenomyosis are at increased risk of multiple obstetric complications, especially early pregnancy losses [1, 5, 9, 10], indicating that the supervision of such women should be more intense and thorough than previously thought and needs

development not only the methods of preconception training, but also the therapeutic and preventive methods of curating pregnant women in the first half of gestation.

The purpose of the study is to conduct a comparative analysis of the influence of different methods of curation of pregnant women on the development of early gestational complications.

Material and methods

There were 89 pregnant women with a pre-radiologically diagnosed adenomyosis (group A). Group A was randomly assigned to two groups AI and AII. The main AI group (n = 45) included women receiving 10 mg twice-daily dydrogesterone twice daily from the time of pregnancy until 20 weeks of gestation; folic acid per os at 400 mcg once a day from the moment of establishment of pregnancy to 12 weeks of pregnancy; solution of L-arginine aspartate per os 5 ml four times daily from 8th to 10th and from 14th to 16th week of pregnancy.

Comparison group AII (n = 44) consisted of women receiving folic acid 400 µg once daily from the time of pregnancy up to 12 weeks of gestation. All patients underwent a complete clinical and laboratory examination in accordance with the existing Ministry of Health of Ukraine orders. In the instrumental examination of women, ultrasound with Doppler scanning was performed using a standard technique using transabdominal and transvaginal convex sensors using ultrasonic devices equipped with devices with a Doppler pulse wave block and a color Doppler function. The echometric parameters of the uterus and ovaries, M-echo, pregnancy, thickness and volume of chorion and placenta at 7-8, 11-12 and 18 weeks of pregnancy were evaluated, resistance index (RI) and pulsation index (PI) of blood flow in spiral were determined and uterine arteries, prenatal fetal condition.

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

The concentration of total nitrite anions (NO_2^-) was determined using a reaction with a Griss-Ilosvay reagent. The quantitative determination of NO_2^- is based on the spectrophotometry of the dye formed in the visible and ultraviolet part of the spectrum, since the resulting dye has an optical density proportional to the concentration of NO_2^- . The

extinction was recorded at a wavelength of 540 nm. The content of free L-arginine in serum was determined by the classical Sakaguchi method, which is based on the mechanism of formation of a stable color complex of orange-red arginine with α -naphthol in the presence of an oxidizing agent. The amount of arginine was calculated according to a calibration graph drawn up in accordance with the conditions of the experiment and which represents the curve of optical density versus the amount of arginine.

Statistical analysis of the results of the study was carried out on a Pentium IV personal computer using the methods of variational statistics and rank correlation using Excel.

Results and Discussion

The duration of pregnancy of a pregnant woman on the doctor in group A was $6,65 \pm 0,07$ weeks of pregnancy, in group AI - $6,60 \pm 0,09$, in group AI - $6,70 \pm 0,12$, in group C - $6,63 \pm 0,09$ and did not differ significantly between groups. The age of pregnant women with adenomyosis of group A averaged 26.62 ± 0.39 years, group AI - 26.49 ± 0.65 , AI - 26.75 ± 0.52 , C - 26.73 ± 0.65 years, $p > 0.05$.

When referring to the doctor, 68.54% of pregnant women with adenomyosis had complaints of pain in the lower abdomen or lower back, of which 68.89% in group AI and 68.18% in group III ($p > 0.05$). Pulling 46.07% and periodic 48.31% pain were preferred. Rarely, pregnant women of group A complained of exercise pain (39.33%), cramping (19.10%) and persistent pain (17.98%).

29.21% of group A pregnant women had first-time complaints of genital bleeding, of which 31.11% in AI group and 27.27% in AII group ($p > 0.05$). In the pregnant study groups, in addition to the complex ultrasound, the chorionic volume was studied with the help of the three-dimensional reconstruction module and with the function of ADF - indicators of uterine-(pre-)placental blood flow and uterine blood flow. As can be seen from the Ttable 1, the volume of chorion in pregnant women with adenomyosis was less than that in pregnant controls - 16.87 ± 0.24 versus $17.58 \pm 0.30 \text{ cm}^3$.

Defective deep placentation in group A at 7-8 weeks of gestation showed an increase in spiral arteries of mean IR of 1.18 and PI - 1.55 times (0.66 ± 0.01 versus 0.56 ± 0.01 ($p < 0.01$) and 1.33 ± 0.02 against 0.86 ± 0.02 ($p < 0.01$)) and mean PI in the uterine arteries - 1.06 times (1.84 ± 0.02 against $1,74 \pm 0.02$ ($p < 0,01$)).

Table 1

Sonographic and Doppler Placental Markers in Pregnant Women at 7-8 Weeks of Gestation

Group	Chorionic volume, cm ³	Mean blood flow in the spiral arteries		Mean index of blood flow in the uterine arteries	
		IR	PI	IR	PI
A, n=89	16,87±0,24 ^c	0,66±0,01 ^c	1,33±0,02 ^c	0,88±0,01	1,84±0,02 ^c
AI, n=45	16,83±0,30 ^c	0,66±0,01 ^c	1,33±0,02 ^c	0,88±0,01	1,83±0,02 ^c
AII, n=44	16,91±0,39 ^c	0,67±0,01 ^c	1,34±0,03 ^c	0,89±0,02	1,85±0,03 ^c
C, n=30	17,58±0,30	0,56±0,01	0,86±0,02	0,87±0,01	1,74±0,02

Notes: 1. ^c – statistically significant difference with Group C scores, p<0,05.

2. No statistically significant difference was found between AI and AII, p>0,05.

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 progesterone concentrations by 1.22 times (21.52 ± 0.57 vs. 26.28 ± 0.55 ng / ml, placental lactogen - 1.21 (0.151 ± 0.003 vs. 0.182 ± 0.009 mg / l), β -HCG - 1.37 (81.50 ± 2.68 vs. 112.07 ± 9.24 ng / ml), free estriol - in 1.28 (1.49 ± 0.04 against 1.90 ± 0.09 nmol / l), PAPP-A - in 1.67 (0.29 ± 0.01 vs $0.48 \pm 0, 05$ mU / l) (Fig. 1).

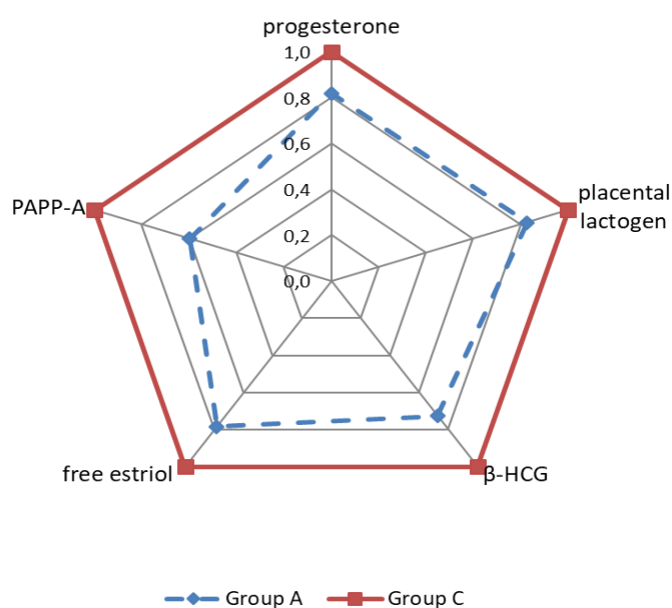


Fig. 1 Offset relative to control indicators of hormones involved in placenta in pregnant women with adenomyosis at 7-8 weeks of gestation.

The nitrosative status of pregnant women with adenomyosis differed by 1.18 times the level of free L-arginine (29.63 ± 0.44 vs. 34.96 ± 0.40 mg / l) and $1.32 - \text{NO}_2^-$ (20.15 ± 0.32 vs 26.51 ± 0.30 $\mu\text{mol} / \text{l}$).

Carrying out prophylactic medical support for early gestation in pregnant women with adenomyosis according to the developed scheme resulted in early miscarriages by the 12th week of pregnancy in 4 pregnant groups of AI and in 12 groups of AII and late miscarriages in 2 and 4 women, respectively. Therefore, a comparative evaluation of the sonographic, Doppler and biochemical parameters studied at 12 weeks of pregnancy was performed between 41 pregnant AI groups and 32 pregnant AI groups and at 18 weeks between 39 pregnant AI groups and 28 pregnant AI groups. Analysis of the study of the dynamics of the presence of pain showed a statistically significant greater efficiency of managing pregnant women with adenomyosis according to the developed scheme (Fig. 2).

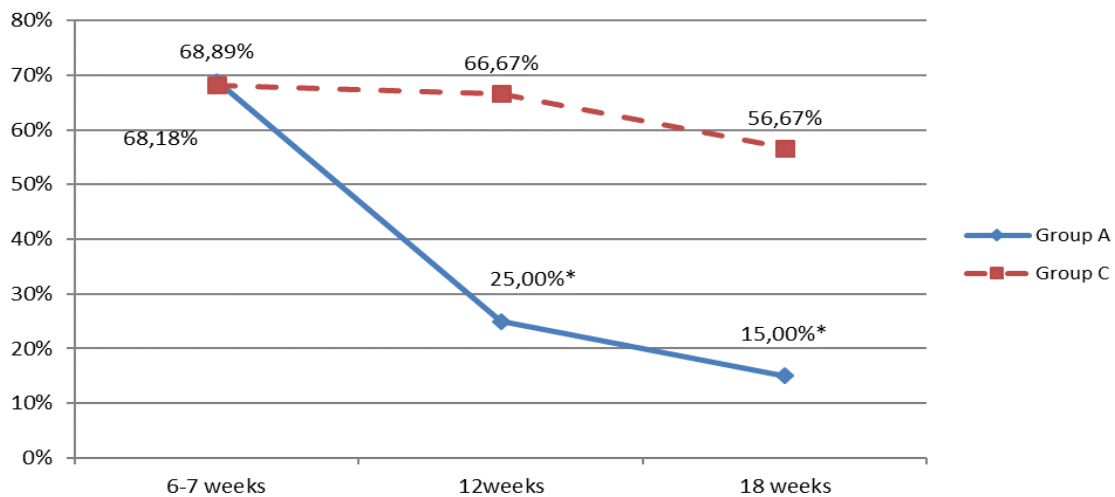


Fig. 2 Dynamics of pain in women with adenomyosis depending on medical support in the early stages of gestation.

Pain syndrome at 12 weeks gestation was observed in pregnant women of AI group 2.67 times less than in group III - 25.00 vs. 66.67% (OR 0.17; 95% CI 0.06 -0.47; $p < 0.01$); at 18 weeks 3.78 times - 15.00 vs. 56.67% (OR 0.14; 95% CI 0.04-0.42; $p < 0.01$).

An analysis of the dynamics of chorionic and placental volumetry indices in ultrasound data in women with adenomyosis depending on medical support in early gestation revealed a statistically significant decrease in placental volume compared with controls at 12 and 18 weeks of gestation in AI groups 1.08 and 1.14 times ($83,82 \pm 1,53$ and $178,53 \pm 3,27$ cm^3) and AII - 1,51 and 1,74 times ($60,15 \pm 1,48$ and $117,04 \pm 3,01$ cm^3)) vs. in group C (90.72 ± 1.82 and 204.12 ± 4.09 cm^3) ($p < 0,01$).

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

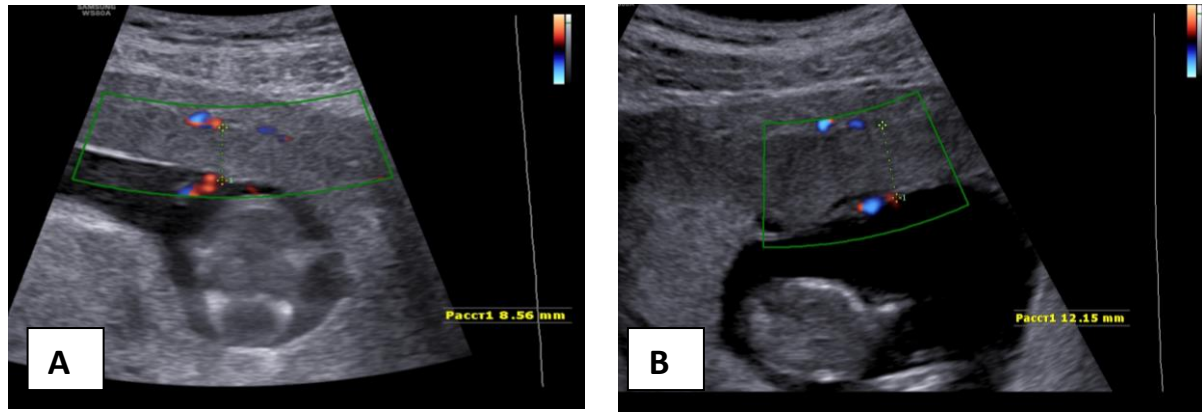


Fig. 3 Ultrasound. A - thinning of the placenta and reducing its volume in women with adenomyosis with the traditional method of pregnancy at 12 weeks of gestation; B is the normal thickness and volume of the placenta in a woman with adenomyosis who has a 12-week gestation schedule.

Analysis of Doppler ultrasound markers of placenta in pregnant women with adenomyosis in the dynamics of the first half of pregnancy showed the advantages of using the developed method of conducting early gestational period in adenomyosis (Fig. 4).

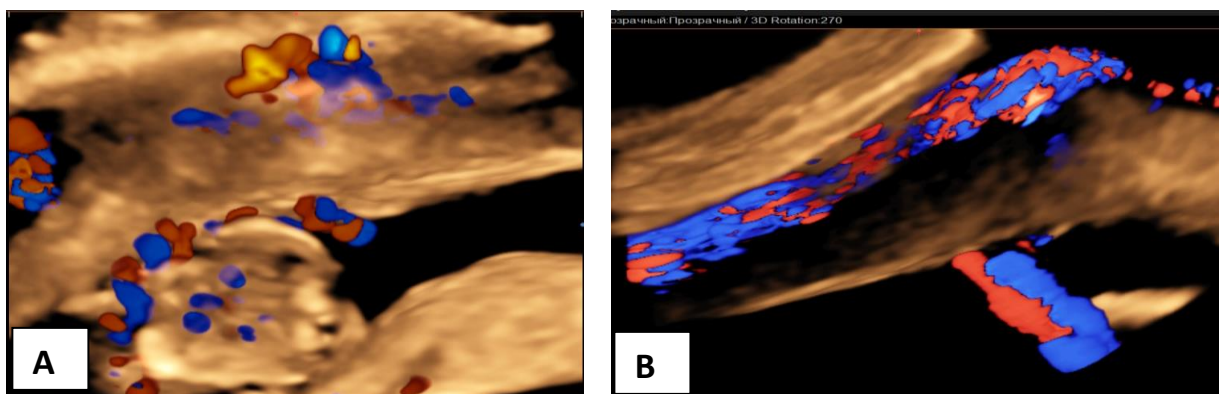


Fig. 4 Color Doppler. A - insufficiency of remodeling of the spiral arteries, which is compensated by increased resistance to blood flow in pregnant group III; B - complete remodeling of the spiral arteries with normal rates of resistance to blood flow in pregnant group AI.

In the AI group, the IR of the spiral arteries in the 11-12 weeks of pregnancy was lower than the same in the group of the AII by 1.08 times (0.56 ± 0.01 versus 0.61 ± 0.01 , $p < 0.02$); at 18 weeks - at 1.10 (0.44 ± 0.01 vs. 0.48 ± 0.01 , $p < 0.01$), and in the uterine arteries - 1.04 times, respectively (0.79 ± 0.02 vs. 0.82 ± 0.01 , $p > 0.05$) and 1.13 (0.59 ± 0.02 vs. 0.67 ± 0.01 , $p < 0.01$). PI was lower in group AI than that in group III in spiral arteries at 1-12 weeks of gestation by 1.08 times (0.85 ± 0.01 vs. 0.92 ± 0.01 , $p < 0.01$); at 18 weeks - at 1.07 (0.66 ± 0.01 vs. 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 1.51 (1.73 ± 0.06 vs. 2.62 ± 0.04 , $p < 0.01$).

The levels and displacement of biochemical markers of placenta in pregnant women with adenomyosis relative to the control in the dynamics of the first half of pregnancy, depending on medical support, were conducted (Table 2).

Table 2

Levels of biochemical markers of placenta in pregnant women with adenomyosis depending on medical support, $M \pm SE$

Hormone	Research Term	Group AI	Group AII	Group C
PAPP-A, mU/ml	7-8 weeks	$0,31 \pm 0,01^c$	$0,26 \pm 0,01^c$	$0,48 \pm 0,05$
	11-12 weeks	$2,31 \pm 0,02^{c,all}$	$2,02 \pm 0,04^{c,al}$	$2,66 \pm 0,09$
	18 weeks	$7,78 \pm 0,31^{all}$	$6,55 \pm 0,40^{c,al}$	$8,29 \pm 0,28$
Estriol, ng/ml	7-8 weeks	$1,51 \pm 0,05^c$	$1,48 \pm 0,07^c$	$1,90 \pm 0,09$
	11-12 weeks	$6,18 \pm 0,24^{c,all}$	$5,43 \pm 0,35^{c,al}$	$6,63 \pm 0,24$
	18 weeks	$14,82 \pm 0,58^{all}$	$12,74 \pm 0,38^{c,al}$	$15,47 \pm 0,53$
β -HCG, ng/ml	7-8 weeks	$79,63 \pm 3,55^c$	$83,42 \pm 4,03^c$	$112,07 \pm 9,24$
	11-12 weeks	$32,02 \pm 2,30^{c,all}$	$27,29 \pm 1,39^{c,al}$	$36,17 \pm 2,26$
	18 weeks	$6,92 \pm 0,42^{c,all}$	$4,61 \pm 0,34^{c,al}$	$8,87 \pm 0,51$
Placental lactogen, mg/l	7-8 weeks	$0,155 \pm 0,005^c$	$0,146 \pm 0,009^c$	$0,182 \pm 0,009$
	11-12 weeks	$0,656 \pm 0,009^{c,all}$	$0,586 \pm 0,008^{c,al}$	$0,728 \pm 0,013$
	18 weeks	$2,715 \pm 0,052^{c,all}$	$1,670 \pm 0,090^{c,al}$	$2,987 \pm 0,078$
Progesterone, ng/ml	7-8 weeks	$21,32 \pm 0,79^c$	$21,71 \pm 0,84^c$	$26,28 \pm 0,55$
	11-12 weeks	$32,43 \pm 0,51^{c,all}$	$30,30 \pm 0,88^{c,al}$	$35,92 \pm 0,39$
	18 weeks	$42,95 \pm 0,77^{all}$	$37,90 \pm 0,81^{c,all}$	$43,13 \pm 0,20$

Note. ^{c, al, all} - statistically significant difference with groups C, AI, AII ($p < 0,05$).

As can be seen from the Table 2, the management of pregnant women according to the developed method led to normalization in group AI at 18 weeks of pregnancy such indicators as PAPP-A, estriol, progesterone, while in group AII none of the studied markers of placenta did not normalize.

The effectiveness of the developed method of managing pregnant women with adenomyosis was shown by the fact that in group AI serum progesterone levels at 11-12 weeks of pregnancy were statistically significantly higher than those in group III by 1.07 times (32.43 ± 0.61 vs. 30.30 ± 0.88 ng / ml) and at 18 weeks by 1.13 (42.95 ± 0.77 vs. 37.90 ± 0.81 ng / ml); placental lactogen - by 1.12 (0.66 ± 0.01 vs. 0.59 ± 0.01 mg / l) and by 1.63 (2.71 ± 0.05 vs. 1.67 ± 0.09 mg / l); β -HCG – by 1.17 (32.02 ± 2.30 vs 27.29 ± 1.39 ng / ml) and by 1.50 (6.92 ± 0.42 vs 4.61 ± 0.34 ng / ml); of free estriol - by 1.14 (6.18 ± 0.24 vs. 5.43 ± 0.35 ng / ml) and by 1.16 (14.82 ± 0.58 vs. 12.74 ± 0.38 ng / ml); PAPP-A - by 1.14 (2.31 ± 0.02 vs. 2.02 ± 0.04 mU / ml) and by 1.19 (7.78 ± 0.31 vs. 6.55 ± 0.40 mU) / ml).

The application of the developed method of managing pregnant women in group AI resulted in normalization of the studied indices of nitrate homeostasis, such as free L-arginine and NO_2^- at 18 weeks of pregnancy. Indicators of nitrate homeostasis in the traditional management of pregnant women with adenomyosis were statistically significantly different from those in control throughout the first half of pregnancy (Table 3).

Table 3

Nitrate status of peripheral blood in pregnant women with adenomyosis depending on medication support, M \pm SE

Hormone	Research Term	Group AI	Group AII	Group C
Free L-arginine, mg/l	7-8 weeks	29,01 \pm 0,55 ^c	30,26 \pm 0,70 ^c	34,96 \pm 0,40
	11-12 weeks	34,14 \pm 0,55 ^{c,all}	31,88 \pm 0,71 ^{c,al}	38,35 \pm 0,40
	18 weeks	46,91 \pm 0,36 ^{all}	41,17 \pm 0,37 ^{c,al}	47,85 \pm 0,37
NO_2^- , nmol/l	7-8 weeks	20,34 \pm 0,49 ^c	19,97 \pm 0,39 ^c	28,72 \pm 0,44
	11-12 weeks	24,38 \pm 0,63 ^{c,all}	22,86 \pm 0,54 ^{c,al}	24,16 \pm 0,68
	18 weeks	29,72 \pm 0,44 ^{all}	28,62 \pm 0,30 ^{c,al}	29,43 \pm 0,25

Note: ^{c, al, all} - statistically significant difference with groups C, AI, AII (p<0,05).

At 11-12 weeks of gestation, the levels of L-arginine in group AI exceeded those in group AI by 1.07 times (34.14 ± 0.55 vs. 31.88 ± 0.71 mg / l, p<0.03) and at 18 weeks, at 1.18

(46.91 ± 0.36 vs. 41.17 ± 0.37 mg / l, p<0.01); and NO₂- at 1.07 (24.38 ± 0.63 vs. 22.86 ± 0.54 nmol / l, p <0.01) and at 1.19 (29.72 ± 0.44 vs. 28, 62 ± 0.30 nmol / l, p<0.01).

The use of the developed method of pregnancy management in women with adenomyosis led to a statistically significant reduction of complications in the first half of pregnancy: the threat of termination of pregnancy by 2.56 times (22.22 vs. 56.82%, p<0.01; OR 0.22; 95% CI 0.09-0.55), the number of cases of retrochorial hematoma - in 2.13 (15.55 vs. 34.09%, p<0.04; OR 0.36; 95% CI 0.13-0.99), early miscarriage - 3.07 (8.89 vs. 27.27 %, p<0.02; OR 0.26 ; 95% CI 0.08-0.88), late miscarriages - 2.05 (4.44 vs. 9.09 %, p>0.05; OR 0.47; 95% CI 0,08-2,68), total miscarriages - in 2,73 (13,39 vs. 36,36%, p<0,01; OR 0,27; 95% CI 0,09- 0.77) (Table 4).

Table 4

Early complications of pregnancy in women studied, n(%)

Indicator	Group AI	Group AII	Group C
The threat of termination of pregnancy	10(22,22) ^{c, aII}	25(56,82) ^{c, aI}	1(3,33)
Retrochorial hematoma	7(15,55) ^{c, aII}	15(34,09) ^{c, aI}	0(0,00)
Early pregnancy toxicosis	3(6,67)	4(9,09)	1(3,33)
Miscarriage early	4(8,89) ^{c, aII}	12(27,27) ^{c, aI}	0(0,00)
Miscarriage late	2(4,44)	4(9,09)	0(0,00)
Total miscarriages	6(13,39) ^{c, aII}	16(36,36) ^{c, aI}	0(0,00)
Iron deficiency anemia	16(35,56)	19(43,18)	7(23,33)

Note: ^{c, aI, aII} - statistically significant difference with groups C, AI, AII (p<0,05).

Conclusions

The use of the developed method of pregnancy management in women with adenomyosis has led to a statistically significant reduction in complications in the first half of pregnancy: the threat of abortion is 2.56 times (OR 0.22; 95% CI 0.09-0.55), the number of cases of retrochorial hematoma - 2.13 (OR 0.36; 95% CI 0.13-0.99), early miscarriages - 3.07 (OR 0.26; 95% CI 0.08-0.88), late miscarriages - 2.05 (OR 0.47; 95% CI 0.08-2.68), total miscarriage - 2.73 (OR 0.27; 95% CI 0.09-0.77).

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