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Pregnancy and Delivery Management in Women with Adenomyosis and Prevention of Gestational Complications

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Abstract: Over recent years, there has been a growing interest in exploring the relationship between adenomyosis and unfavorable pregnancy outcomes in the field of reproductive medicine. The aim of this study is to assess various strategies for managing pregnancy in women with adenomyosis to mitigate the risk of gestational complications. Our findings underscore the need for a tailored approach to pregnancy care and thorough preconception preparation to enhance maternal and fetal outcomes.

Keywords: adenomyosis, pregnancy, obstetric complications.

Adenomyosis is a prevalent condition among women of reproductive age, characterized by the presence of endometrial glands and stroma within the myometrium of the uterus. Recent research has demonstrated the detrimental effects of adenomyosis on women's reproductive function, including reduced fertility and increased pregnancy and delivery complications[1, 3, 4, 6, 7]. Several well-accepted theories explain the reproductive dysfunction associated with adenomyosis, such as alterations in endometrial and myometrial structure and function, impaired sperm transport, dysfunctional uterine contractions, and heightened oxidative stress levels within the uterus[1, 5, 9, 12]. Adenomyosis serves as a valuable model for predicting various pregnancy and childbirth complications due to its well-studied nature and ongoing clinical observations. Studies have highlighted the negative impact of adenomyosis on assisted reproductive technologies, resulting in lower pregnancy success rates and higher miscarriage rates. Furthermore, adenomyosis is frequently linked to complications like preterm delivery and premature rupture of membranes, necessitating close monitoring of pregnant women with adenomyosis for potential gestational complications.

The presence of adenomyosis may impede the invasion of extravillous trophoblast cells into the uterine spiral vessels, potentially leading to placental dysfunction, preeclampsia, and preterm birth. Moreover, ectopic endometrial foci disrupt hormonal regulation, intercellular communication, and immune processes within the uterine mucosa, negatively impacting decidualization, placentation, and fetal development. The mechanisms underlying placental development disturbances in the context of pathological pregnancy, childbirth, and perinatal complications related to adenomyosis are not yet fully understood. These issues may stem from inadequate adaptive changes and remodeling of the uterine wall preceding implantation and placental development, potentially leading to long-term consequences in line with Barker's hypothesis. Therefore, investigating the impact of adenomyosis on offspring is warranted.

Recent studies have shown that women with adenomyosis face over a threefold higher risk of preterm delivery and fetal growth restriction, along with a fourfold increased risk of preeclampsia. These complications typically arise in the first trimester of pregnancy. Significant alterations have been observed during biochemical screening and Doppler ultrasound of the

uterine artery in cases of diffuse adenomyosis. Specifically, pregnant women with diffuse adenomyosis exhibited notably lower levels of PAPP-A and higher uterine artery pulsation index in the first and second trimesters compared to healthy individuals or those with focal adenomyosis. These impaired placental processes were associated with a nearly fivefold increased likelihood of fetal growth restriction specifically in cases of diffuse adenomyosis. Consequently, close monitoring and potential drug interventions are necessary for pregnant women with adenomyosis to prevent fetal growth restriction syndrome and preeclampsia.

Progesterone plays a crucial role, particularly during the preconception period, for women with adenomyosis. Achieving complete secretory transformation of the endometrium and optimal trophoblast invasion leading to the formation of a well-functioning placenta are key predictors of a successful pregnancy outcome. It is advisable for women with a history of recurrent miscarriages to consider routine progesterone supplementation during the luteal phase of the menstrual cycle before conception and up to 8-10 weeks post-conception to support a healthy pregnancy. A systematic review of 14 studies involving 2158 women with a history of recurrent miscarriage revealed a substantial decrease in the risk of recurrent pregnancy loss with the use of progesterone, showing no variance in maternal and fetal adverse events compared to placebo or no treatment. This evidence was confirmed by a meta-analysis conducted by Hamdan et al.

The endometrium plays a crucial role in pregnancy, as it harbors a vast network of blood vessels that support the essential structures and cells required for implantation and trophoblast function. Despite normal hormone levels, some patients may still encounter challenges with inadequate growth and functionality of the endometrium. Research indicates that elevated peripheral vascular resistance within the uterine vasculature triggers reduced proliferation and vascular endothelial growth factor production in the endometrium, leading to decreased glandular layer growth and vasculogenesis in the presence of adenomyosis.

Ensuring sufficient endometrial thickness and optimal function is vital in women with adenomyosis to enhance pregnancy rates and promote healthy gestation. This necessity calls for further exploration into interventions that can positively influence these aspects, particularly addressing the challenges of insufficient angiogenesis and blood circulation within the functional endometrial layer. Consequently, discussions around preconceptional endometrial preparation and management strategies during gestation in women with adenomyosis remain contentious.

In light of these considerations, to minimize obstetric complications during pregnancy in women with adenomyosis, it is imperative to undertake preconceptional endometrial preparation to facilitate implantation and placental processes, alongside providing progesterone support in the first trimester.

The aim of this study was to compare different approaches to managing pregnancy in women with adenomyosis to prevent gestational complications.

Materials and Methods:

A comparative prospective study was conducted on 103 pregnant women with adenomyosis aged 25 to 44 years (average age of 36.6 ± 4.2 years). Based on adenomyosis severity and treatment method, participants were categorized into two groups: Group 1 with 82 women having grade I–II adenomyosis and Group 2 with 21 women with grade III adenomyosis. After adenomyosis treatment, pregnancy planning was initiated. Subsequently, the pregnant women were further subdivided into subgroups based on management: Subgroup A (n = 37) received micronized progesterone at 600 mg daily and acetylsalicylic acid at 150 mg daily to prevent gestational complications until 16 weeks of pregnancy; Subgroup B (n = 29) followed traditional management methods. Additionally, a comparison group of 112 pregnant women without adenomyosis was included. Inclusion criteria encompassed confirmed adenomyosis, while exclusion criteria encompassed diffuse adenomyosis, grade 4 adenomyosis, uterine fibroids, uterine malformations, severe somatic conditions, and acute pelvic inflammatory diseases.

During the study, participants underwent clinical and laboratory assessments, ultrasound examinations, and Doppler assessments of uterine vessels. Statistical analysis involved descriptive statistics using Excel 2013, with frequency distributions and Fisher's angular transformation for percentage comparisons. Quantitative data were described using mean (M) and standard deviation (SD). Two-tailed Student's t-test was employed to compare independent groups on a single criterion. Statistical analyses were conducted using Microsoft Office Excel 2013 and Statistica 6.0, with significance set at $p < 0.05$.

In the research findings, among the 103 pregnant women studied, 79.6% had grade 1-2 adenomyosis, while 20.4% had grade 3. The average age across groups was 36.6±4.2 years, with a higher prevalence of women aged 40 years and older in the grade III adenomyosis group (19.1%) compared to the grade I-II group (6.7%) ($p<0.05$). Infertility duration varied significantly based on adenomyosis severity, with 4.1±0.7 years for grade I-II adenomyosis and 9.6±2.4 years for grade III adenomyosis.

The infertility structure also differed: grade III adenomyosis showed a higher occurrence of long-term primary infertility (38.1%) compared to grade I-II adenomyosis (15.9%) ($p<0.05$). Conversely, secondary infertility was more prevalent in grade I-II adenomyosis (84.1%) compared to grade III (61.9%) without significant difference.

Assessment of preconception preparation effectiveness post-adenomyosis therapy was based on pain and menstruation duration, Doppler parameters of uterine vessels, pregnancy rates, and subsequent pregnancy outcomes. Clinical improvements were observed in both groups, with a reduction in pain and menstruation duration observed in 68.3% and 61.9% of patients, respectively. Regression of pelvic pain (visual analogue scale) by the end of therapy was noted in 74.3% of participants in the grade I-II group and 61.9% in the grade III group.

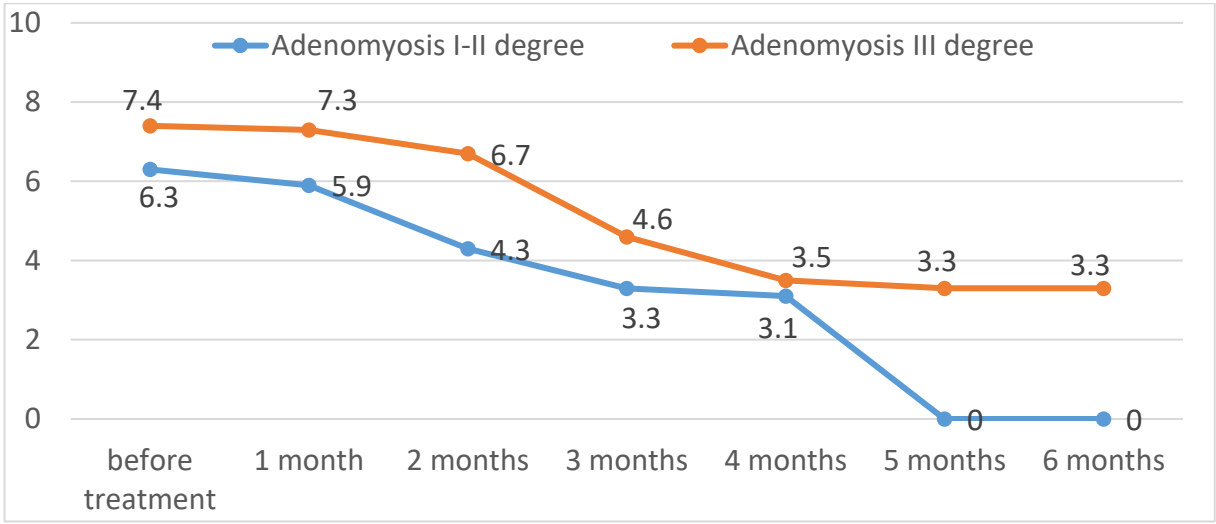

Figure 1: Resistance index values in uterine vessels before and after therapy (M±m).

A study on blood circulation parameters in uterine vessels among different grades of adenomyosis showed significant differences pre- and post-therapy. Dynamic evaluation of uterine hemodynamics in women with grade I-II adenomyosis indicated normalization of blood flow indicators in various segments of the uterine vascular bed in 47.6% of cases, and in grade III adenomyosis, this normalization was seen in 28.6% of cases. These changes likely contributed to the favorable outcomes of in vitro fertilization (IVF).

Arteries	1st group with adenomyosis I-II degree (n=82)		2nd group with adenomyosis III degree (n=21)	
	Before treatment	After	Before treatment	After
Right uterine artery	0,85±0,12	0,82±0,06	0,88±0,07	0,85±0,10
Left uterine artery	0,85±0,10	0,81±0,06	0,87±0,09	0,86±0,10

Arcuate artery	0,76±0,16	0,70±0,07*	0,80±0,14	0,76±0,08
Radial arteries	0,70±0,06	0,64±0,06*	0,72±0,04	0,70±0,05
Basalarteries	0,64±0,05	0,60±0,04*	-	0,64±0,05*
Spiral arteries	0,57±0,04	0,52 ±0,03*	-	0,55±0,02*

After treatment of adenomyosis with dienogest for 6 months, significant improvement in blood flow was observed in the arcuate, basal, and spiral arteries of the uterus, as indicated in Table 1.

The asterisk (*) denotes a significant difference in resistance index values before and after treatment ($p<0.05$).

Following therapy, the next phase of the study involved planning pregnancy to alleviate symptoms of the pathology and enhance uterine vascular circulation. Within a year post-therapy, 64.1% of the 103 women became pregnant, with 68.3% of those with grade I-II adenomyosis conceiving compared to 47.6% with grade III adenomyosis. The comparison group comprised 112 pregnant women without adenomyosis.

Literature highlights the complex course of pregnancy in women with adenomyosis, including increased risk of miscarriage in both early and late stages. To mitigate miscarriage risk and ensure proper implantation, angiogenesis, and placentation processes, pregnant women with adenomyosis were prescribed micronized progesterone at 600 mg daily and acetylsalicylic acid at 150 mg daily up to 16 weeks of pregnancy.

Comparative analysis of gestational outcomes revealed an 89.1% live birth rate in the adenomyosis group, whereas the comparison group showed a higher rate of 98.6% (Table 2). Reproductive losses included spontaneous miscarriages, non-progressing pregnancies, antenatal fetal death, very early and early preterm births, leading to early neonatal mortality in both groups.

Table 2. Pregnancy outcomes in women with adenomyosis

Outcomes	Pregnant women with adenomyosis (n=66)		Pregnant women without adenomyosis (n=112)	
	abs	%	abs	%
Spontaneous miscarriages	7	10,6	8	7,1
Non-developing pregnancies	6	9,1**	3	2,7
Very early and early premature delivery	7	10,6**	3	2,7
Premature delivery	10	15,2*	11	9,8
Antenatal fetal death	3	4,5	-	-
Live births	47	88,7	99	98,0
Stillbirth	6	11,3**	2	1,8

Notes: * - difference in the indicators of the group with adenomyosis relative to the values of the group of women without adenomyosis (* - $p<0.05$; ** - $p<0.001$).

Pregnancy outcomes in women with adenomyosis were marked by certain complications. Spontaneous miscarriages occurred in 10.6% of cases among women with adenomyosis and in 7.1% of women without adenomyosis, showing no statistically significant difference. Non-developing pregnancies were observed in 9.1% of women with adenomyosis, predominantly beyond 11-12 weeks of gestation, which was 3.4 times more frequent than the 2.7% rate in

women without adenomyosis. This could be attributed to disruptions in implantation and angiogenesis processes associated with adenomyosis, as supported by existing literature.

The most common issues during the latter part of pregnancy were very early and early premature deliveries, with a frequency of 10.6% in women with adenomyosis—3.9 times higher than in women without adenomyosis. The comparison group had no very early preterm births, with only 2.7% of cases ending in early preterm birth around 28-29 weeks of pregnancy. Overall, the incidence of all preterm births was 25.8% in pregnant women with adenomyosis, which was twice as high as the 12.5% rate in women without adenomyosis. Additionally, antenatal fetal death was observed in 4.5% of women with adenomyosis, with causes including premature abruption of a normally located placenta (3.0%) and fetal growth restriction syndrome (1.5%).

These complications were predominantly seen in pregnant women with adenomyosis who did not receive prophylactic treatment with micronized progesterone and acetylsalicylic acid. The examination aimed to evaluate the effectiveness of preventing gestational complications in women with adenomyosis by assessing pregnancy progression and outcomes within study groups.

Table 3. Features of the course of pregnancy in women with adenomyosis, depending on management

Complications	Pregnant women with adenomyosis who received complex prophylaxis (n=37)		Pregnant women with adenomyosis managed traditionally (n=29)		Pregnant women without adenomyosis (n=112)	
	Abs	%	abs	%	abs	%
Threat of miscarriage	13	35,1*▲	19	65,5*	19	17,0
Spontaneous miscarriages	3	8,1▲	4	13,8*	8	7,1
Non-developing pregnancies	1	2,7▲▲	5	17,2*	3	2,7
Placental dysfunction	9	24,3▲	14	48,3*	22	19,6
Hypertensive disorders	7	18,9	8	27,6*	16	14,3
Severe preeclampsia	2	5,4*▲	3	10,3*	1	0,9
Fetal growth restriction syndrome	1	2,7▲▲	4	13,8*	2	1,8
Antenatal fetal death	0	0	3	10,3	0	0
Premature abruption of a normally located placenta	0	0	2	6,9*	1	0,9
Placenta previa	3	8,1*	2	6,9*	0	0
Premature delivery, of which:	6	16,2▲	11	37,9*	14	12,5
Premature delivery at 22-33 weeks	2	5,4*▲▲	5	17,2*	3	2,7
Premature delivery >34 weeks	4	10,8▲	6	20,7*	11	9,8

C-section	8	21,6	9	31,0*	21	18,8
Anomalies of labor	7	18,9*	7	24,1*	13	11,6
Postpartum hemorrhage	9	24,3*▲	11	37,9*	18	16,1
Anomal attachment of the placenta	3	8,1*	3	10,4*	5	4,5
Subinvolution of the uterus	12	32,4*▲	16	55,2*	25	22,3

Note: * - difference in indicators of women in groups with adenomyosis, relative to the comparison group without adenomyosis (* - $p<0.05$; ** - $p<0.001$); ▲ - difference in the indicators of groups with adenomyosis that received prophylaxis compared to the group treated traditionally (▲ - $p<0.05$; ▲▲ - $p<0.001$).

A study on the progression of pregnancy in women with adenomyosis revealed that despite preventive measures, the course of pregnancy was complex. Among women with adenomyosis, more than half experienced a threat of miscarriage, amounting to 65.5%. In pregnant women with adenomyosis who received prophylactic treatment, the threat of miscarriage was observed in 35.1%, which was 1.9 times lower than in women without prophylaxis, but still 2.1 times higher than in pregnant women without adenomyosis.

The risk of miscarriage was further complicated by spontaneous miscarriages and premature births in 13.8% and 37.9% of women with adenomyosis who received traditional management, which was 1.7 (8.1%) and 2.3 (16.2%) times higher than the rates of pregnant women undergoing prevention. Notably, the values of the group of women who received prophylaxis did not significantly differ from the group of pregnant women without adenomyosis.

Pregnant women with adenomyosis who were traditionally managed had a higher occurrence (17.2%) of very early and early premature births, which was 3.2 times higher than in the group receiving prophylaxis.

In pregnant women with adenomyosis (Table 3), a significant ($p<0.05$) increase in the frequency of hypertensive disorders was observed - 27.6% (comparison group - 14.3%), along with severe preeclampsia in 3 (10.3%) women, placental dysfunction with impaired fetal hemodynamics - 48.3% (comparison group - 19.6%), and fetal growth restriction syndrome - in 13.8% (comparison group - 1.8%). A study on the progression of pregnancy in women with adenomyosis found that, despite preventive measures, the course of pregnancy was complex. Among women with adenomyosis, more than half experienced a threat of miscarriage, amounting to 65.5%. In pregnant women with adenomyosis who received prophylactic treatment, the threat of miscarriage was observed in 35.1%, which was 1.9 times lower than in women without prophylaxis, but still 2.1 times higher than in pregnant women without adenomyosis.

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(comparison group - 19.6%), and fetal growth restriction syndrome - in 13.8% (comparison group - 1.8%).

With prophylaxis using micronized progesterone and acetylsalicylic acid, the frequency of these complications in women with adenomyosis decreased and did not significantly differ from the values in the group of women without adenomyosis. It should also be noted that antenatal fetal death (10.3%) only occurred in the group of women with adenomyosis who did not receive preventive prophylaxis.

The study of the course of labor showed a high frequency of complications, including weakness of labor (24.1% and 18.9%) and abnormal tight attachment of the placenta (10.4% and 8.1%). The rate of cesarean sections in women with adenomyosis without prophylaxis was higher than population rates (31%), with emergency surgeries required for various complications.

Postpartum hemorrhage was observed in more than 1/3 of women (37.9%) with adenomyosis managed traditionally and in 24.3% who received prophylaxis, which is 1.6 times more often. The postpartum period in women with adenomyosis was also characterized by high rates of uterine subinvolution.

In summary, the presence of adenomyosis poses significant challenges during pregnancy and childbirth, and preventive measures such as prophylactic treatment can help reduce the frequency of complications, although some risks still remain elevated compared to women without adenomyosis.

The data from this study indicates that pregnant patients with adenomyosis are at an increased risk of early reproductive losses and premature births ($p<0.05$). Additionally, they are more likely to experience placental dysfunction with hemodynamic disturbances and fetal growth restriction syndrome during pregnancy ($p<0.05$). The frequency of hypertensive disorders, including preeclampsia, is almost doubled in pregnant women with adenomyosis. Furthermore, complications during labor and the postpartum period significantly increase in frequency ($p<0.05$), particularly weakness of labor and postpartum hemorrhage. These complications are largely associated with the structural features of the endometrium-myometrium transition zone, which may be related to the invasion of the endometrium into the myometrium.

It is suggested that the increased ability of the endometrium to proliferate in women with adenomyosis, regardless of its degree of spread, may lead to disturbances in the remodeling of spiral arterioles, resulting in abnormal transformation and defective differentiation of placental structures. This ultimately contributes to the obstetric complications observed in women with adenomyosis.

In conclusion, women with adenomyosis exhibit an elevated frequency of reproductive losses, complications during pregnancy, childbirth, and the postpartum period, highlighting the importance of early detection and timely correction of this pathology as part of preconception preparation.

The study also found that pregnancy occurred in 64.1% of women after treatment for adenomyosis, with a higher occurrence in women with adenomyosis I-II degrees (68.3%) compared to those with adenomyosis III degree (47.6%). The course of pregnancy in women with adenomyosis was complicated by high rates of reproductive losses, including spontaneous miscarriages, non-developing pregnancies, antenatal fetal death, and early neonatal mortality. Common complications during pregnancy and childbirth in women with adenomyosis included placental dysfunction, hypertensive disorders, premature birth, postpartum hemorrhage, fetal growth retardation syndrome, placenta previa, abnormal placental attachment, and uterine subinvolution. This underscores the need for a more individualized approach to pregnancy management and high-quality pre-pregnancy preparation.

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