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Clinical and anamnestic data and morphofunctional characteristics of the endometrium in women with uterine developmental anomalies

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BACKGROUND: Uterine developmental anomalies have a negative impact on the implementation of female reproductive function, leading to a high risk of reproductive failures, premature birth, placental insufficiency, intrauterine growth retardation syndrome, labor anomalies and postpartum bleeding. The presence of both structural anomalies themselves and the high frequency of reproductive failures leads to repeated intrauterine interventions, which are considered as a premorbid background for the endometrial pathology development. Despite the combined causes of reproductive failure, morphological studies of the endometrium in women with various uterine anomalies are scarce.

AIM: The aim of this study was to evaluate the clinical and anamnestic data and morphological characteristics of the endometrium in women with uterine anomalies and reproductive failures in the anamnesis.

MATERIALS AND METHODS: We examined 123 women with uterine developmental anomalies (49 patients with an arcuate uterus, 38 patients with a uterine septum, 16 patients with a bicornuate uterus, 10 patients with an unicornuate uterus, 10 patients with dimetria). Standard clinical and laboratory work-up, hysteroscopy with endometrial biopsy and laparoscopy were performed in all patients. Histological and immunohistochemical examination of the endometrium was carried out according to the standard technique with assessment of the relevant receptor profile (estrogen and progesterone receptors) and pro-inflammatory markers ($CD8^+$, $CD20^+$, $CD4^+$, and $CD138^+$).

RESULTS: Clinical and anamnestic data evaluation in patients with uterine anomalies revealed menstrual abnormalities, commonly, dysmenorrhea. Regardless of the type of uterine anomaly, a high incidence of pelvic inflammatory disease, endometriosis and a high frequency of reproductive failures were found. The morphological structure of the endometrium with uterine anomalies was characterized by a higher frequency of endometrial hyperplasia, impaired secretory transformation and the presence of chronic endometritis.

CONCLUSIONS: Patients with a variety of uterine developmental anomalies are characterized by menstrual irregularities, a high incidence of gynecological pathology and reproductive failures. There is no association between pathognomonic signs of endometrial morphofunctional abnormalities and the type of uterine anomaly; however, they are similar to those seen in recurrent miscarriages and infertility of various origins.

Keywords: uterine malformation; defect; secretory endometrial transformation; chronic endometritis; reproductive loss.

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Клинико-анамнестические данные и морфофункциональные особенности эндометрия у женщин с аномалиями развития матки

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Обоснование. Аномалии развития матки негативно влияют на реализацию репродуктивной функции женщины, приводя к высокому риску репродуктивных потерь, преждевременным родам, формированию плацентарной недостаточности, задержке внутриутробного развития плода, аномалиям родовой деятельности и кровотечениям в послеродовом периоде. Как сами структурные аномалии, так и высокая частота репродуктивных потерь служат причиной повторных внутриматочных вмешательств, формируя преморбидный фон для развития патологии эндометрия. Несмотря на сочетанный фактор репродуктивных неудач, морфологические исследования эндометрия при различных аномалиях развития матки единичны и фрагментарны.

Цель — оценить клинико-анамнестические данные и морфологическое состояние эндометрия у женщин с аномалиями развития матки и репродуктивными неудачами в анамнезе.

Материалы и методы. Обследованы 123 пациентки с аномалиями развития матки (49 пациенток с седловидной маткой, 38 пациенток с перегородкой полости матки, 16 пациенток с двурогой маткой, 10 пациенток с однорогой маткой, 10 с удвоением матки). Всем пациенткам выполняли стандартное клинико-лабораторное исследование, гистероскопию с биопсией эндометрия и лапароскопию. Гистологическое и иммуногистохимическое исследование эндометрия проведено по стандартной методике с оценкой рецепторного профиля эндометрия (рецепторы эстрогенов и прогестерона) и провоспалительных маркеров ($CD8^+$, $CD20^+$, $CD4^+$, $CD138^+$).

Результаты. По клинико-анамнестическим данным у пациенток с аномалиями развития матки выявлено нарушение менструального цикла по типу дисменореи. Независимо от вида аномалии матки отмечены высокая частота воспалительных заболеваний органов малого таза, наружного генитального эндометриоза, а также высокая частота репродуктивных потерь. Морфологическая картина эндометрия при аномалиях развития матки характеризуется высокой частотой гиперплазии эндометрия, нарушениями секреторной трансформации эндометрия и наличием хронического эндометрита.

Выводы. Для пациенток с различными видами аномалий развития матки характерны нарушения менструального цикла, высокая частота гинекологической патологии и репродуктивных потерь. Патогномоничные признаки нарушения морфофункциональных характеристик эндометрия в зависимости от вида аномалии матки не прослеживаются, но они сходны с таковыми при привычном невынашивании и бесплодии различного генеза.

Ключевые слова: аномалии развития матки; нарушение секреторной трансформации эндометрия; хронический эндометрит; репродуктивные потери.

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BACKGROUND

Uterine developmental anomalies represent a crucial challenge of modern medicine because of their negative impact on the implementation of normal female reproductive functions [1–5]. During embryogenesis, uterine malformations are known to occur as the impairment of the formation, fusion, or adsorption of Mullerian ducts. Its types can be distinguished depending on the stage of embryogenesis when the anomaly arose; for example, hypoplasia/agenesia of the uterus in the case of absence or underdevelopment of two ducts; unicornuate uterus in the case of underdevelopment or absence of one duct; didelphia or bicornuate uterus in the case of disorder of fusion processes; and arcuate uterus or intrauterine septum in the case of the impairment of canalization processes [6, 7].

A study demonstrated the incidence of uterine malformations as follows: 55% of cases reported intrauterine septum, 10% reported bicornuate uterus, 5%–20% reported unicornuate uterus, 5%–10% reported arcuate uterus, and 5% of the cases reported didelphia [8]. In the general population, the incidence of this pathology reaches 5%–25% and uterine developmental anomalies are often only detected with an impaired reproductive function, thereby making it difficult to establish their true prevalence [9].

L. Fedele et al. (2006) and D. Wold et al. (2006) demonstrated that about 1% of fertile women reported the septum of the uterine cavity (complete and incomplete), which is characterized by negative reproductive results as compared with other forms of uterine developmental anomalies [10, 11]. The arcuate uterus is considered as a variant of the norm; however, it often leads to an incorrect fetal position. Furthermore, the unicornuate uterus, bicornuate uterus, and didelphia mildly increase the risk of premature birth [12].

The causes of the negative impact of uterine developmental anomalies on the reproductive process are still unknown. It is assumed that the probable causes of reproductive losses may be attributed to the disorders in the morphofunctional state of the endometrium, pathology of implantation, and uncoordinated contractions of the myometrium [13].

At the same time, morphological studies of the endometrium with various anomalies of the uterus are sporadic and fragmentary. At present, it has not been established whether reproductive losses are associated with an impaired morphofunctional state of the endometrium at the stage of embryogenesis or whether the impairment of endometrial morphogenesis occurs because of the combined factors of intrauterine interventions and the formation of endometrial dysfunction.

The objective of this study is to evaluate the clinical and anamnestic data along with the morphological condition of the endometrium among women with uterine developmental anomalies and a history of reproductive failures.

MATERIALS AND METHODS

In total, 123 patients with uterine anomalies, who underwent examination and, if necessary, surgical treatment in gynecological department I (with an operating unit) of D.O. Ott Research Institute of Obstetrics, Gynecology, and Reproductology were included in this study. Five groups were formed depending on the shape of the anomalies:

- group 1 included 49 patients with an arcuate uterus;
- group 2 included 38 patients with an intrauterine septum;
- group 3 included 16 patients with a bicornuate uterus;
- group 4 included 10 patients with a unicornuate uterus;
- group 5 included 10 patients with didelphia.

All patients underwent standard clinical laboratory examination, hysteroscopy, and laparoscopy. Endometrial biopsy was performed during hysteroscopy in phase 1 (day 8–10) of the menstrual cycle in 43 patients and in phase 2 of the menstrual cycle (day 19–24) in 78 patients. The histological examination of endometrial biopsies was performed according to the standard technique. Hematoxylin and eosin staining was used for review staining. The studies were performed on an Olympus CX31 microscope (Japan) at magnifications of 100×, 200×, and 400×. Immunohistochemical study was performed according to the standard one-stage protocol with antigen retrieval (high-temperature tissue treatment) in 0.01 M of citrate buffer and a pH of 7.6. Dako Cytomation LSAB2 System-HRP (Dako, Denmark) was used as the imaging system. The immunohistochemical study included a quantitative and qualitative assessment of the expression of estrogen and progesterone receptors (ER and PR) and pro-inflammatory markers ($CD8^+$ [cytotoxic T-lymphocytes], $CD20^+$ [B-lymphocytes], $CD4^+$ [T-helpers], and $CD138^+$ [plasma cells]) using primary antibodies in standard dilutions according to the recommended protocol. The expression of sex hormone receptors was assessed by Histochemical Score = $\Sigma P(i) \cdot I$, where i is the intensity of staining, expressed in points from 0 to 3; $P(i)$ is the proportion of cells stained with different intensities (%). The nature of distribution of the expression of receptors was considered in the test material (even, uneven). The severity of chronic endometritis was determined according to the classification presented by G.Kh. Tolibova et al. (2015) [14].

Statistical analysis of the data was performed using the STATISTICA 10 software (StatSoft, Inc.). The normality of distribution was tested using the Shapiro–Wilk test. Normally distributed data were presented as mean (M) ± standard error of the mean (m). Student's t-test was used to compare the results. The results were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

The average age of the patients, regardless of the form of uterine developmental anomaly, did not differ statistically and was 32 ± 0.40 (23–44) years. The body mass index corresponded to the norm in 90% of cases and averaged 22.7 ± 0.3 kg/m^2. The analysis of anthropometric data in patients, regardless of the form of anomaly, and the analysis of menstrual function demonstrated that the age of menarche, the duration of the menstrual cycle and its continuance within the groups were comparable (from 12 to 18 years) and did not have statistical differences. The duration of the menstrual cycle varied from 23 to 40 days and averaged 28.6 ± 0.24 days. The average duration of menstruation was 3–8 days.

An irregular menstrual cycle was registered in the 30 (24.8%) patients. For example, the irregular menstrual cycle was observed in every fourth patient with an arcuate uterus (24.5%), every fifth patient (17.9%) with an incomplete intrauterine septum, three (18.7%) patients with a bicornuate uterus, and five patients with a unicornuate uterus (50%). Dysmenorrhea was detected in every third (15) patient with an arcuate uterus (30%) and with a bicornuate uterus (6, 37.5%). It was also noted with the same frequency in patients with unicornuate uterus and didelphia (3 cases each, 30%). Dysmenorrhea was detected in 14 patients (36.8%) with an intrauterine septum. Abundant uterine bleeding was registered in every third patient with a bicornuate uterus (5, 31.3%), every third patient with didelphia (4, 40%), every fourth patient with an intrauterine septum (8, 21.1%), every tenth patient with an arcuate uterus (5, 10.2%), and every fifth patient with a unicornuate uterus (2, 20%). Opsomenorrhea was noted with didelphia in 4 cases (40%), 2 cases in patients with an arcuate uterus (4.1%) and bicornuate uterus (12.5%), and 1 patient with an intrauterine septum (2.6%). However, opsomenorrhea was not detected in patients with unicornuate uterus.

Concomitant gynecological pathology was represented by the inflammatory diseases of the pelvic organs (salpingo-oophoritis, chronic endometritis, and adhesions of the pelvic organs), external genital endometriosis of varying severities, and uterine myoma (intramural and intramural–subserous forms). Chronic salpingo-oophoritis was verified in five (14.3%) patients with an arcuate uterus, five (13.2%) patients with an intrauterine septum, four (40%) patients with didelphia, and one (6.3%) patient with a bicornuate uterus. Importantly, chronic salpingo-oophoritis was not detected in patients with a unicornuate uterus. External genital endometriosis was diagnosed in every fourth patient with an arcuate uterus (26.5%) and a bicornuate uterus (25%), every third patient with an intrauterine septum (31.6%) and a unicornuate uterus (30%), and every second (50%) patient with didelphia. Uterine myoma was detected in 7 (18.4%) women with an intrauterine septum, 5 (10.2%) women with an arcuate uterus, and 1 (10%) woman with didelphia. Importantly, it was not detected in patients with a bicornuate uterus or unicornuate uterus.

According to the literature, uterine developmental anomalies are quite often concomitant with genital endometriosis; for example, 18.5% of women with an intrauterine septum, 7.7% with didelphia, and 29.4% of patients with a bicornuate uterus had uterine developmental anomalies [15, 16]. In contrast, A. Demir (2011) did not reveal a significant difference in the incidence of external genital endometriosis in patients with an intrauterine septum and normal uterine anatomy, along with a history of infertility and miscarriage [17]. Patients with uterine developmental anomalies often have comorbidities of the urinary tract [18, 19]. Our research results show that diseases of the urinary system (chronic pyelonephritis, chronic cystitis, and urolithiasis) were registered in less than 10% of cases in all the groups.

It is noteworthy that infertility was the most common complaint of patients. Infertility lasting from 1 to 15 years was registered in 66 (53.7%) women. Primary infertility was noted in 46 (37.4%) of these women, in which 19 (38.8%) patients had an arcuate uterus, 10 (26.3%) patients had an intrauterine septum, 4 (25%) cases had a bicornuate uterus, 8 (80%) patients had a unicornuate uterus, and 5 (50%) patients had didelphia. Moreover, secondary infertility was registered in 20 (16.3%) women. Furthermore, in these women, 8 (16.3%) patients had an arcuate uterus, 7 (18.4%) patients had an intrauterine septum, 3 (18.7%) cases had a bicornuate uterus, 1 (10%) patient had a unicornuate uterus, and 1 (10%) patient had didelphia.

It is well known that uterine developmental anomalies are accompanied by a high risk of reproductive loss, premature delivery, placental insufficiency, intrauterine growth retardation, an early discharge of amniotic fluid, and abnormalities of labor and bleeding in the postpartum period [20–22].

The results of the anamnestic study showed that pregnancy ended in delivery at term in four patients with an arcuate and bicornuate uterus, four patients with an intrauterine septum, and one patient with a unicornuate uterus. A history of an induced termination of pregnancy was registered in three patients with an intrauterine septum and an arcuate uterus and in three patients with a bicornuate uterus. Ectopic pregnancy developed in four patients with an arcuate uterus, as well as in two patients with an intrauterine septum and didelphia. In addition, a high frequency of reproductive losses was registered (Table 1).

In all the groups, irrespective of the form of uterine anomaly, spontaneous miscarriages occurred significantly more often as compared with non-developing pregnancy in trimester I ($p < 0.01$).

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Table 1. The structure of reproductive losses in the groups under study

Group	Total amount of reproductive losses in trimester I (*n* = 117)		Non-developing pregnancy		Spontaneous miscarriage		Terms of abortion, weeks
	n	%	*n*	%	*n*	%	*M* ± *m*
Group 1, arcuate uterus (*n* = 49)	40	34.2	13	26.5	27	55.1*	6.3 ± 0.62
Group 2, intrauterine septum (*n* = 38)	58	49.6	18	31.0	40	68.9**	8.5 ± 0.61*
Group 3, bicornuate uterus (*n* = 16)	10	8.5	3	30.0	7	70.0**	5.7 ± 1.14
Group 4, unicornuate uterus (*n* = 10)	2	1.7	0	0	2	1.7	7.5 ± 0.3
Group 5, didelphia (*n* = 10)	7	5.9	2	28.6	5	71.4**	7.1 ± 0.8

* $p < 0.05$, ** $p < 0.01$ when compared within groups.

Table 2. Morphological structure of the endometrium in the patients of the examined groups

Группа	Correspondence with the phase of the menstrual cycle		Endometrium developmental delay		Endometrial hyperplasia		Endometrial polyp	
	n	%	*n*	%	*n*	%	*n*	%
Group 1, arcuate uterus (*n* = 49)	28	57.1	10	20.4	11	22.4	6	12.4
Group 2, intrauterine septum (*n* = 38)	20	52.6	13	34.2	5	13.2	9	23.7
Group 3, bicornuate uterus (*n* = 16)	6	31.2	3	18.7	7	43.7	3	18.7
Group 4, unicornuate uterus (*n* = 10)	4	40.0	2	20.0	4	40.0	2	20.0
Group 5, didelphia (*n* = 10)	5	50.0	3	30.0	2	20.0	1	10.0

In case of an intrauterine septum, the termination of pregnancy at a term of 8.5 ± 0.61 weeks was probably associated with a disorder of synchronization of the gravidic transformation of the endometrium of the uterine cavity, the endometrium of the septum of the uterine cavity, and the anatomical and topographic aspects of the uterine cavity.

Because of reproductive losses and obstetric complications, there is a need for repeated intrauterine interventions that undoubtedly cause the development of chronic endometritis, impaired endometrial receptivity, and the combination of these factors subsequently determines endometrial dysfunction [23].

According to the results of histological examination of endometrium, the correspondence of the endometrium structure to the phase of the menstrual cycle was revealed in 57.1% of patients with an arcuate uterus, 52.6% of patients with intrauterine septum, and 50% of patients with didelphia (Table 2).

The data presented here indicate that the morphofunctional state of endometrium is impaired in patients with uterine anomalies. Endometrial hyperplasia without atypia, detected in every fifth patient with an arcuate uterus and didelphia as well as in every second patient with a bicornuate uterus and a unicornuate uterus, can serve as an independent factor of infertility.

According to the combination of histological (mononuclear infiltration, fibrosis of the stromal component, vascular sclerosis) and immunohistochemical studies (an increase in the number of cytotoxic T-lymphocytes [$CD8^+$], B-lymphocytes [$CD20^+$], T-helpers [$CD4^+$], and plasma cells [$CD138^+$]), chronic endometritis of varying severities was verified in 78 (63.4%) patients. Among these patients, mild endometritis was found in 10 (8.13%) cases, moderate endometritis was found in 45 (36.6%) cases, and severe endometritis was found in 23 (18.7%) cases.

Chronic endometritis was detected in 32 (65.3%) patients with an arcuate uterus, 22 (57.9%) patients with intrauterine septum, 12 (75%) patients with a bicornuate uterus, 6 (60%) patients with a unicornuate uterus, and 6 (60%) patients with didelphia. The presence of a glandular polyp of the endometrium and a high frequency of chronic endometritis of varying severities represent the determining

factors in the inadequate gravidic transformation of the endometrium.

Based on the assessment of the expressions of ER and PR, an uneven distribution and a decrease in the expressions of ER and PR in the stromal component of the endometrium (a multifocal decrease in expression less than 70 points) was registered in 31 cases (25.2%). Among these patients, 10 (20, 4%) patients had arcuate uterus, 13 (34.2%) had intrauterine septum, 3 (18.7%) had a bicornuate uterus, 2 (20%) cases had a unicornuate uterus, and 3 cases (30%) had didelphia. A comparative analysis of the receptor profile between uterine abnormalities was not performed, because about 50% of endometrial biopsy samples did not correspond to the phase of the menstrual cycle and chronic endometritis was verified in more than 60% of cases in all groups.

V.O. Gashenko (2012) also revealed a higher incidence of chronic endometritis and a decrease in the expression of ER and PR in the endometrium covering the septum. According to the author, these changes can cause infertility and miscarriage in patients with an intrauterine septum [24].

At the same time, pathognomonic signs of a disorder of the endometrium's morphofunctional characteristics, depending on the type of uterine anomaly, are not traced. Regardless of the variants of uterine anomaly, the expression of receptors in the endometrium decreases in the presence of chronic endometritis with the formation of fibrosis and fibroplastic changes in the stromal component, which probably result from intrauterine interventions due to the termination of pregnancy and concomitant pathology.

Thus, according to the clinical and anamnestic data of patients with uterine developmental anomalies, a high frequency of inflammatory diseases of the pelvic organs, external genital endometriosis, reproductive losses, and intrauterine interventions associated with abortion were revealed. The above facts collectively form a premorbid background for the development of endometrial pathology. An impairment of the endometrium's morphofunctional characteristics with uterine developmental anomalies is similar to that with the recurrent miscarriage and infertility of various origins, when endometrial dysfunction is formed.

It can be assumed that the impairment of the endometrium's morphofunctional state is a reversible or conditionally reversible process because the patients have a history of childbirth and the onset of pregnancy occurs after the surgical correction (removal of the septum) and treatment of concomitant pathology (inflammatory diseases of the pelvic organs, and external genital endometriosis). The obtained results of this complex morphological study should be analyzed to identify additional factors in the pathology of reproductive function among patients with uterine developmental anomalies.

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