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ORIGINAL

Genetic aspects of gynaecological diseases: new approaches to diagnosis and treatment

Aspectos genéticos de las enfermedades ginecológicas: nuevos enfoques de diagnóstico y tratamiento

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ABSTRACT

Currently, there is no consensus among experts regarding the causes of gynaecological diseases. It is hypothesized that various environmentales factors, such as an unhealthy lifestyle (smoking, overeating, and lack of physical activity), may influence the development of gynaecological diseases. Therefore, the aim of the work will be to investigate the genetic aspects of gynecological diseases, from diagnostic methods to treatment. However, the hypothesis of genetic origin is considered particularly important in the etiopathogenesis of gynecological diseases. The main strategies for identifying and treating women's health ailments with a genetic component have been examined. Although numerous studies have been conducted, the regulation of the reproductive system and the pathogenesis of hormone-dependent pathologies are still not fully understood. These problems are complex and relevant in both the scientific sphere and practical medicine. In gynecological practice, the most frequent conditions among women of reproductive age are fibroids, adenomyosis, and ovarian cysts. These conditions often require radical surgery. Recently, there has been a trend of younger patients experiencing disruptions in their reproductive function, often resulting in infertility ranging from 30-80 %. The clinical presentation of the disease is severe, with prolonged and heavy bleeding, complications, and progressive pain. This can lead to a loss of work capacity and psychoemotional disorders. Therefore, this issue is extremely relevant. At the time of examination, the duration of the disease ranged from 1 to 10 years. Patients reported complaints of heavy or prolonged menstruation, menstrual cycle disturbances, lower abdominal pain, and infertility. The clinical picture and patients' complaints indicate a genetic association with the disease.

Keywords: Genetic Aspects; Gynaecological Diseases; Diagnosis; Treatment.

RESUMEN

En la actualidad, no existe consenso entre los expertos sobre las causas de las enfermedades ginecológicas. Existe la hipótesis de que diversos factores ambientales, como un estilo de vida poco saludable (fumar, comer en exceso y la falta de actividad física), pueden influir en el desarrollo de las enfermedades ginecológicas. Sin embargo, la hipótesis del origen genético se considera especialmente importante en la etiopatogenia de las enfermedades ginecológicas. Se han examinado las principales estrategias para identificar y tratar las

dolencias de la salud femenina con un componente genético. Aunque se han realizado numerosos estudios, la regulación del sistema reproductor y la patogénesis de las patologías hormono dependientes aún no se comprenden del todo. Estos problemas son complejos y relevantes tanto en el ámbito científico como en la medicina práctica. En la práctica ginecológica, las afecciones más frecuentes entre las mujeres en edad reproductiva son los miomas, la adenomiosis y los quistes ováricos. Estas afecciones suelen requerir una intervención quirúrgica radical. Recientemente, se ha observado una tendencia a que las pacientes más jóvenes experimenten alteraciones en su función reproductora, lo que a menudo provoca una infertilidad que oscila entre el 30 y el 80 %. La presentación clínica de la enfermedad es grave, con hemorragias prolongadas y abundantes, complicaciones y dolor progresivo. Esto puede llevar a una pérdida de la capacidad laboral y a trastornos psicoemocionales. Por lo tanto, este tema es extremadamente relevante. En el momento del examen, la duración de la enfermedad oscilaba entre 1 y 10 años. Las pacientes se quejaban de menstruaciones abundantes o prolongadas, alteraciones del ciclo menstrual, dolor abdominal bajo e infertilidad. El cuadro clínico y las quejas de las pacientes indican una asociación genética con la enfermedad.

Palabras clave: Aspectos Genéticos; Enfermedades Ginecológicas; Diagnóstico; Tratamiento.

INTRODUCTION

At the start of the third millennium, ovarian cancer remains a challenging gynecological oncological disease caused by genetic factors. In Ukraine, the incidence of ovarian cancer is 16,4 per 100 000 population, with a mortality rate of 9,8 per 100 000 population. The age range of ovarian cancer patients varies from 40 to 60 years and older, with the peak incidence of the disease in Ukraine occurring at the age of 60-64 years. Numerous studies focus on identifying molecular links in the pathogenesis of uterine hyperplastic diseases. However, the mechanisms behind the development of uterine fibroids and adenomyosis are not yet fully understood. Recently, there has been a global increase in the number of patients with these pathologies. Up to 85 % of cases involve a combination of these two diseases occurring against the background of endometrial hyperplastic processes.

Endometriosis is a chronic disease that poses many questions to clinicians and is a pressing issue in modern gynaecological practice. Statistics prove that approximately 170 million women worldwide suffer from endometriosis. The frequency of this pathology in women of reproductive age varies widely, from 7 to 50 %, with a recent steady increase noted. Despite its high social significance, effective therapy is still lacking. In 1992, at the III World Congress on Endometriosis in Brussels, this condition was renamed “a new disease of civilization”. Endometriosis is a chronic, dyshormonal, immune-dependent disease with benign tissue diversity that is genetically determined. New directions in the conservative treatment of uterine fibroids are the use of ulipristal acetate, which is a selective modulator progesterone receptors, for adenomyosis dienogest – progesterone fourth generation with selective activity of 19-nortestosterone and progesterone. Currently carried out in all european countries scientific research on the use of these two drugs to treat fibroids and adenomyosis confirm its effectiveness.[1,2] However, combined pathology requires further study of issues of etiology and pathogenesis in in the light of new scientific research.

Uterine fibroids and adenomyosis are genetic pathologies that develop due to various factors and genetic predisposition. Some researchers suggest a link between myometrial and endometrial diseases in their pathogenesis.[3,4,5,6] When combined, the clinical manifestations of uterine fibroids and adenomyosis have more pronounced symptoms than when they occur in isolation. This is because both pathologies share common pathogenetic mechanisms of development and mutually stimulate pathological processes. Uterine fibroids and adenomyosis share similar symptoms, including pelvic pain, genital bleeding, and uterine enlargement. This similarity creates difficulties in diagnosis and treatment. Many questions regarding the aetiology, diagnosis, and therapy of these combined pathologies remain unresolved.

Literature review

Foundational works on identifying hereditary forms of ovarian cancer and genetic heterogeneity include the works of Lynch et al.[7] They noted that approximately 18 % of oncological patients with a family history have relatives affected by cancer, especially in the female reproductive system. Early diagnosis of ovarian cancer is difficult due to the lack of pathogen-clinical symptoms in the initial stages of the disease. Ovarian cancer is diagnosed in its late stages in 70 % of patients due to the asymptomatic course of the disease in the early stages. The progression of the disease mainly occurs through dissemination from the peritoneum. This explains the asymptomatic course of the disease in the early stages.

Franks et al.[8] proposed the hypothesis of genetic determinism of gynaecological diseases, which is of particular interest. This theory suggests that genetically determined ovarian pathology is characterized by excessive androgen production. Excess androgens can influence the hypothalamic-pituitary-gonadal axis of

the fetus during the embryonic period, which may trigger a series of adverse factors leading to the onset of gynaecological disease during the sexual maturation of girls.[9]

According to Lewy et al.[10] girls who are genetically predisposed to insulin resistance and excessive weight are more susceptible to developing gynaecological diseases during adolescence. At the same time, the aetiology of various forms of disorders of the development and functioning of the female reproductive system is a priority area of reproductive medicine and one of modern medicine and genetics.[11] Features of gynaecological ovarian disease that have different long-term consequences for women's health:

1) hyperandrogenism (excess androgen) + oligo-anovulation + polycystic ovarian morphology (PCOM).
2) hyperandrogenism + oligo-anovulation.
3) hyperandrogenism + PCOM.
4) oligo-anovulation + PCOM.[12,13,14,15,16]

Women diagnosed cardiovascular diseases, and other metabolic complications. Additionally, they may experience infertility and endometrial cancer. About 60-70 % of patients with PCOS are overweight or obese, and obesity is associated with insulin resistance. However, research has shown that insulin resistance can also be present in women with ovarian gynaecological diseases, even without obesity (figure 1).[17,18,19]

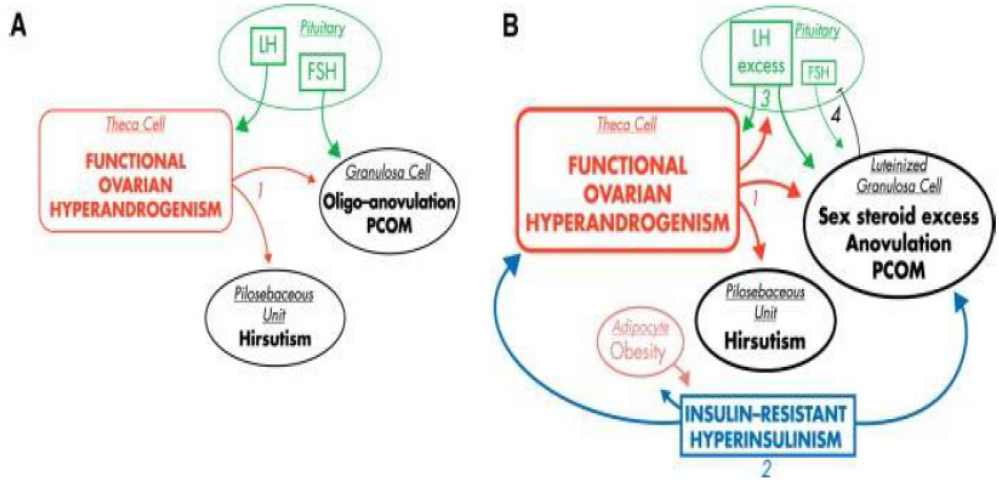

Figure 1. Pathophysiology of gynaecological ovarian disease

Ovulation disorders, including irregular ovulation or complete absence, account for around 30 % of all causes of female infertility. According to Castro et al.[20] gynaecological diseases of the ovaries are the primary cause of anovulatory infertility, constituting approximately 70 %. Patients with gynaecological diseases of the ovaries may have an increased risk of miscarriages and pregnancy complications, such as gestational diabetes, due to hormonal imbalances.

Scientific research [21] has shown that approximately one in four patients with uterine fibroids has myocytes with increased mitotic activity. There are two clinical-morphological variants of uterine fibroids: simple and mitotically active or proliferating fibroids. The rapid growth of myomatous nodes and pronounced clinical manifestations of the disease in proliferating uterine fibroids can be explained by the development of neovascularization. Recently, there has been research into the pathogenesis of various gynaecological diseases,[22] including uterine fibroids, with a focus on disturbances in intercellular interactions. Additionally, scientists are searching for markers of endometriosis among hormones, analyzing the levels of estrogen, progesterone, prolactin, FSH, and LH in women with this condition. However, there is controversy surrounding the pathogenesis, diagnosis, and treatment of uterine fibroids and adenomyosis.

The aim of this study is to analyze the use and justification of technologies for diagnosing and treating gynecological diseases, while considering genetic factors. Additionally, international approaches to the diagnosis and treatment of gynecological diseases in women will be described.

METHOD

This study 165 women analyzed with a combined form of uterine fibroids and adenomyosis, polycystic ovary syndrome, and ovarian cancer. It examined the clinical course of the diseases and the reproductive function statuses of the women. The patients under observation underwent several diagnostic procedures, including ultrasound examination with colour Doppler mapping of uterine arteries, intra- and perinodal blood flow analysis of adenomyotic and myomatous nodes, immunological examination, and histological examination of removed uteri from operated women diagnosed with uterine fibroids, adenomyosis, and combinations of

fibroids with ovarian cancer.

In women with suspected adenomyosis and uterine fibroids, identified by collection of complaints and anamnesis, during a gynecological examination, diagnosis was confirmed by ultrasound examination of the pelvic organs.[23,24] The study was conducted on MINDRAY DC7 devices, sensor type and frequency C 5-2 and ESAOTE Mylabe 7c, sensor type VC2541, with a frequency of 3,5 MHz. (series of longitudinal and transverse sections using a device operating on the principle of "gray scale" on the device). High frequencies of ultrasound sensors allowed diagnose areas of adenomyosis that portable devices cannot could "see" and differentiate fibroid nodes from adenomyotic nodes (which were previously described on ultrasound as myomatous nodes), location, the number and size of nodes, with combined forms, determined the shape adenomyosis which is most combined with fibroids, multiple or single nodes.

The study involved conducting detailed questionnaire surveys and collecting information on past illnesses, childhood infectious diseases, and any concomitant gynecological and extragenital diseases. Additionally, the menstrual function history, obstetric and gynecological history of the patients under examination, and their disease development history were also analyzed. The study included women with infertility caused by various factors, and both partners were examined to rule out male factor infertility. The gynecological status of all women was assessed during the examination, therapy, and rehabilitation. Ethical aspects were observed during the experiment.

RESULTS

All patients admitted for surgery underwent a routine examination, including a general blood count, a complete blood count, a coagulogram, immunological tests, a blood chemistry test, a general smear test (three-point smear test), and a bacteriological examination of the microflora with antibiotic susceptibility testing.

In a retrospective study (table 1), 301 patients who were offered surgery were analyzed. Indications for surgery in these patients were mainly diagnosed with symptomatic uterine fibroids, the main symptom of which was abnormal uterine bleeding in 89 %.

Table 1. Indications for surgical treatment (retrospective study)

Diagnosis	Quantity	%
Uterine fibroids	140	46,5
Ovarian cysts	94	31,2
Ectopic pregnancy	20	6,7
Abnormal uterine bleeding	47	15,6
Total number of patients	301	100

Prospective studies were conducted on 165 reproductive-aged patients under observation, who were divided into 3 groups after examination:

1st group – 75 patients with uterine fibroids;

2nd group – 47 patients with ovarian cysts;

3rd group – 43 patients with uterine fibroids and ovarian cancer.

The control group consisted of 21 healthy women.

The age of the patients corresponded to the reproductive age criteria of the WHO and ranged from 20 to 45 years old. The average age was as follows: in the 1st group – 38,4±0,48 years, in the 2nd group – 35,1±0,89 years, in the 3rd group – 37,5±0,88 years, and in the control group – 34,8±1,27 years, meaning the groups were equivalent and comparable (table 2).

Table 2. Age of the examined patients

Age	Control group, n = 21		1st group, n=75		2nd group, n=47		3rd group, n=43	
	Qty.	%	Qty.	%	Qty.	%	Qty.	%
20-24	-	-	-	-	3	6,4±3,6	1	2,3±2,3
25-29	4	19,1±8,8	3	4,0±2,3	4	8,5±4,1	3	7,0±3,9
30-34	10	47,6±11,2	8	10,7±3,6**	11	23,4±6,2	8	18,6±6,0*
35-39	2	9,5±6,6	28	37,3±5,6**	19	40,4±7,2**	13	30,2±7,1*
40-45	5	23,8±9,5	36	48,0±5,8*	10	21,3±6,0	18	41,9±7,6
Average age	34,8±1,27		38,4±0,48*		35,1±0,89		37,5±0,88	

Note: *- significantly compared to the control group (*-P<0,05; **-P<0,01)

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Acute respiratory infections were the most common past illnesses in all three groups, with pneumonia being more common than bronchitis. However, the frequency of these illnesses was significantly higher (P<0,001) in the main groups compared to the control group. Childhood infectious diseases were 1,7 times less common in the third group than in the first and second groups. Between 90,7 % and 95,7 % of patients in all groups experienced diseases of the upper and lower respiratory tract, such as tonsillitis, pharyngitis, bronchitis, and acute respiratory infections. The analysis of previously experienced illnesses and current somatic diseases revealed that the majority of patients had two or more illnesses in their medical history.

It is noteworthy that patients in the 1st group had a significantly higher frequency (6,5 times higher) of cervical pathology (61,3±5,6 %, p<0,001) compared to the control group (Table 3). Additionally, in the 3rd group of patients with uterine fibroids, ovarian cysts were noted with a frequency 2,5 times lower than in the control group. It is suggested that risk factors for the development of gynaecological diseases include a complex medical history, a high disease index during the reproductive period (including genetic factors), childhood infectious diseases, menstrual cycle disorders, inflammatory diseases of the uterus, and a high frequency of abortions or intrauterine interventions.

Table 3. Frequency of gynaecological diseases in the anamnesis

Nosology		Pathologies of the cervix	Curettage of the uterine cavity	Ovarian cysts	Other
Control group, n = 21	Qty.	2	-	-	-
	%	9,5±6,6	-	-	-
1st group, n=75	Qty.	46	24	18	3
	%	61,3±5,7***	32,0±5,4***	24,0±5,0***	4,0±2,3
2nd group, n=47	Qty.	19	7	11	1
	%	40,4±7,2**	14,9±5,3*	23,4±6,2**	2,1±2,1
3rd group, n=43	Qty.	16	22	4	-
	%	37,2±7,5*	51,2±7,7***	9,3±4,5*	-

Note: * - significantly compared to the control group (*-P<0,05; **-P<0,01; ***-P<0,001)

In cases of combined endometriosis with chronic cervicitis, focal lymphoid infiltration and moderately pronounced koilocytosis were observed in the mucous membrane, indicating viral involvement of the cervix (HPV) and referred to as LSIL (figure 2).

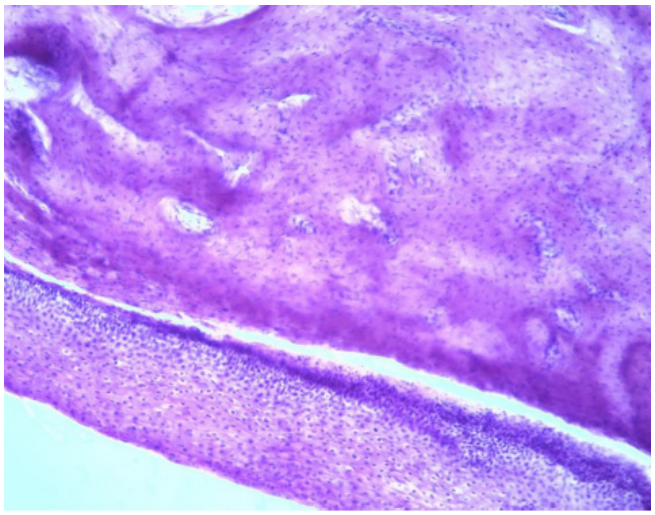

Figure 2. Patient M, 42 years old. Focal lymphoid infiltration of the mucous membrane of the vaginal part of the cervix. Moderately pronounced koilocytosis is observed. Stained with hematoxylin and eosin. Magnification 10x10

High rates of induced abortions were observed in the third group, and almost three times higher control group. Furthermore, the total number of miscarriages in all three groups exceeded that of the control group by several times. The frequency of spontaneous pregnancy loss in combination with pathology was almost five times higher than that of the control group. Patients with isolated uterine fibroids also reported a history of miscarriage (5,1 %). This incidence was three times higher than that of the control group. The reproductive history of the patients in all three main groups showed a high overall number of pregnancies. Therefore, we also considered the genetic aspect of ovarian cysts, which strongly affects the onset and course of pregnancy (table 4).

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Table 4. Main complaints of patients

Nosology	1st group, n=75		2nd group, n=47		3rd group, n=43	
	Qty.	%	Qty.	%	Qty.	%
Hyperpolymenorrhea	51	68,0±5,4	16	34,0±7,0*	23	53,5±7,7
Pelvic pain and algomenorrhea	49	65,3±5,5***	31	66,0±7,0***	7	16,3±5,7
Violations menstrual cycle	52	69,3±5,4***	20	42,6±7,3**	6	14,0±5,4
Dyspareunia	33	44,0±5,8*	14	29,8±6,7	11	25,6±6,7
Total infertility	21	28,0±5,2	12	25,5±6,4	7	16,3±5,7
Of them						
Primary infertility	14	66,7	4	33,3	3	42,9
Secondary infertility	7	33,3	8	66,7	4	57,1

Note: * - significantly compared to the control group (*-P<0,05; **-P<0,01; ***-P<0,001)

During ultrasound examination of examined patients assessed the presence of myomatous nodes in the uterus, indicating their sizes, quantity, topography and type, as well as the presence of adenomyotic foci. Ultrasound also made it possible to determine the size of myomatous and/or adenomyotic uterus. The therapeutic approach for ovarian cysts should be tailored to the specific aetiology and clinical presentation of the condition. The strategy should focus on lifestyle modifications, reduction of androgen secretion and action, improvement of metabolic status in women. It should be stressed that despite significant progress in the diagnosis and treatment of ovarian cysts, many issues related to the pathogenesis and associated metabolic and reproductive disorders still remain ambiguous and controversial.

DISCUSSION

Numerous studies indicate a close connection between endometriosis and changes in the immune system. The latter concern both humoral and cellular immunity. It is possible that suppression of the immune system by immunotoxic substances facilitates implantation of endometrial cells in ectopic sites in cases of retrograde menstruation and induces the development of endometriosis. There is evidence that endometrioid cells become resistant to lysis due to the expression of HLA class antigens on their surfaces, which suppress the lytic activity of natural killer cells. It is possible that genetic defects of NK cells, which lose the ability to recognize and lyse ectopically located endometrioid cells, may act as the primary pathological link.

Ultrasound examination is used worldwide as a screening test to detect gynecological pathologies, especially uterine fibroids and ovarian cysts. This method enables visual determination of the presence and proliferative activity of uterine fibroid nodules and adenomyosis foci, as well as the location of nodules and foci of adenomyosis. Additionally, the use of colour Doppler mapping allows for assessment of the quality of blood flow within (intranodularly) and around (perinodularly) fibroid and adenomyosis nodules, as well as in the uterine arteries in cases of diffuse forms of adenomyosis. During the ultrasound examination, the presence of uterine fibroid nodules and adenomyosis foci were assessed, including their size, quantity, topography, and type. The sizes of the fibroid and/or adenomyosis uterus were determined using ultrasound.

Chemotherapy, along with surgical methods, is considered an important component in the treatment of patients with ovarian cancer. Clinicians determine the need for chemotherapy at all stages of the disease. Preoperative chemotherapy is recommended for massive tumour involvement of the peritoneum and large omentum with signs of infiltration into the anterior abdominal wall. After evaluating the effect of chemotherapy, cytoreductive surgery is performed. Radiotherapy has been used for ovarian cancer since the early 20th century and has undergone complex development. For many years, attempts have been made to use various types and methods of radiotherapy for ovarian tumours. These include deep X-ray therapy, manual applicators of cobalt and radium, internal and intracavitary administration of radioactive preparations, and distant gamma therapy. Radiotherapy is commonly used as an additional treatment method for patients with tumours that have not responded to chemotherapy, or for patients with recurrences after primary treatment, including chemotherapy and surgery. It can also be useful for palliative treatment of incurable patients with symptomatic gynaecological diseases or distant metastases.

It is important to note that endometriosis can involve the uterine myometrium in a pathological manner, typically during a preserved menstrual cycle. The presence of uterine fibroids in combination with adenomyosis has minimal impact on the clinical manifestations of the disease, except for submucosal fibroid nodules. Patients with uterine endometriosis and endometrial hyperplasia may experience menometrorrhagia or acyclic bloody discharge. Based on a comparison of the clinical characteristics of the disease with the results of histological examination removed during surgery, our analysis indicates that pathognomonic manifestations of adenomyosis are characteristic of the II-III degree of the spread of the process, as well as its nodular form.

CONCLUSIONS

Ovarian cysts remain one of the most prevalent gynaecological conditions affecting women of reproductive age in Ukraine. The current situation requires the implementation of effective measures to predict the risk of developing gynaecological diseases using high-tech methods such as molecular-genetic analysis of markers of hormonal and metabolic disorders. Additionally, treatment programs should be introduced to restore natural fertility and increase the effectiveness of programs like IVF.

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CONFLICT OF INTEREST

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