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Genital biotope in infertile women with cervical intraepithelial neoplasia.

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Abstract
The article presents the characteristics of genital biotope of 250 women with cervical intraepithelial neoplasia (CIN) under disorders of reproductive function.
The state of vagina and cervical canal microbiocenosis in women surveyed indicates the presence of opportunistic pathogenic flora, sexually-transmitted infections and viral infection of the genital organs under CIN in women with reproductive disorders.
We determined the species spectrotype of microorganisms that indicates the presence of deep disorders in microbiocenosis. This gives us the opportunity to assert that the surveyed female patients under the development of dysplastic cervical processes an infectious factor is of importance, namely association of microorganisms with the presence of HPV of high-speed oncogenic potential with viral load >3 Ig HPV/10^5 cells and allows to treat infectious factor as one of the substantial reasons for impaired reproductive function.

Keywords: genital biotope, cervical intraepithelial neoplasia, infertility.

1. Introduction
Important indicator of female reproductive health is infertility – the reproductive failure of mature body. Disorders of the reproductive function are the consequence of various disorders in the female body, they reduce social and psychological adaptation, affect her health and quality of life [10, 13].
We found out that among the causes of reproductive disorders in women dominate inflammatory diseases of internal genital organs. Inflammatory diseases of pelvic organs due to previously deferred sexually transmitted infections (STIs) are the causes of female infertility in 38% of cases [1, 3, 5]. Chronic inflammatory diseases of uterine, uterine appendages and their after-effects in 40% - 82% of cases are the main reason for the development of tubal-peritoneal infertility [6, 8, 9, 10]. Present in vagina microorganisms, as well as sexually transmitted ones usually initialize inflammatory process. If in the past decade the main attention was focused on the identification of bacterial (Chlamydia, ureaplasma, mycoplasma, anaerobic) infection [4, 7, 14], then in recent period in the study of infertility the importance is attached to persistent forms of chronic viral infections, in particular to the role of human papilloma virus [2, 3, 11]. Infection with human papilloma virus is accompanied by decrease in fertility, development of chronic diseases, infertility and irreversible disorders in organs of the reproductive system, has impacted on the development of pregnancy failure and leads to high perinatal losses [12, 15].
Accurate and up-to-date diagnostics of STIs is important in the general system of infertility prevention and treatment, because infection and inflammatory process contributes to the structural damage and dysfunction of ovaries. In addition, the microorganisms, which are present in the urinogenital system in women with abnormal immunoreactivity, can block sperm cell and affect their mobility, lead to the formation of antispermatic antibodies [4].
Therefore the study of the microbiological aspects in the context of cervical intraepithelial neoplasia in infertile women is necessary to identify one or another factor, or association of factors, which are essential cofactors in its occurrence and progress. This circumstance became the aim of our study.

2. Material and Methods
We conducted comprehensive clinicopathologic study of 250 women with cervical intraepithelial neoplasia (CIN) under disorders of reproductive function. CIN diagnosis was made using the tumours classification by World Health Organization: Pathology and genetics of breast tumours and female genital organs tumours (Travassoli F.A., Devilee, 2003), International classification of diseases of 10th revision (1995), and International histological

classification of tumours by WHO No.13. Depending on the severity of the CIN all the cases were divided into three study groups: the 1st group – 110 cases with mild CIN (CIN-I); the 2nd group – 86 cases of moderate CIN (CIN-II); the 3rd group – 54 cases of severe CIN (CIN-III). The average age of women with dysplastic processes of uterine cervix was 29,4±1,3 years. 58,4% of women suffered from primary infertility 41,6% – from secondary infertility. Among the causes of primary infertility prevailed tubal-peritoneal factor (46,6%), which was detected in 68 women. Among the surveyed women tubal-peritoneal factor, as a primary, was found in 27,2%, hormonal infertility was diagnosed in 37 female patients (14,8%), combined factors occurred in 24 cases (9,6%). In the structure of secondary infertility dominates tubal factor (60,6%), peritoneal infertility was observed in 24,0% of female patients. In women with secondary infertility were not observed reproductive disorders associated with endometriosis, immune genesis and unspecified forms. In the total number of women surveyed secondary tubal infertility constitutes 25,2%, peritoneal – 10,0%, combined infertility was found in 3,6% of female patients.

The control group consisted of 30 women with reproductive disorders, in which under histological examination of cervical biopsies were not revealed any pathology of uterine cervix. The average age of patients in the control group totalled 23,9±0,82 years.

All patients were screened for pathogenic types of genital infections according to clinical protocols (order No. 582 Ministry of Health of Ukraine dated 15.12.2013). To study biotope of uterine cervix we used bacterioscopic, immunoassay, bacteriological and molecular biological methods. Detected pathogens – Chlamydia trachomatis, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, Herpes Simplex Virus II in scraping from the mucous membrane of the cervical canal and uterine cervix surface were determined by polymerase chain reaction (PCR) method ("Amplisens" system test, Russian Federation). All female patients were screened for human papilloma viral infection. For PVI identification in the capacity of the most sensitive method was employed PCR with hybridization-fluorescent detection in real time (Real-Time PCR) with the use of reagents kit (PCR - kit "Amplisens HPV HCR screen-titer-FL" produced by the Central Research Institute of Epidemiology of the Ministry of Health, Russian Federation). The net result was calculated automatically in the logarithms of the genome equivalents of the virus (Ig GE) normalized to 100 thousand (10^5) human genomes. We identified DNA of 12 types (16, 18, 31, 35, 39, 45, 51, 52, 56, 58, 59 types) of human papilloma viral (HPV) of high carcinogenic risk (HCR). Selected types have high oncogenic property regarding neoplastic transformation and development of carcinoma of uterine cervix.

3. Results and Discussion.

While studying the condition of genital biotope of the uterine cervix surface and the mucous membrane of the cervical canal in all cases we noticed a predominance of causative agents associations.

The more frequently we observed an associative form of a combination of Chlamydia, bacterial and fungal infections. Amid a sharp decrease in the proportion of identifying lactic acid bacteria increases the proportion of bacterial and bacterial-viral vaginosis. The species spectrotype of microorganisms found in women with CIN under fertility failure is presented in table 1.

Table 1: The species spectrotype of microorganisms found in women with CIN under fertility failure (abs. nmb.,%).

Microorganisms	Groups under study							
	CIN-I (n=110)		CIN-II (n=86)		CIN-III (n=54)		Control (n=30)	
	abs.	%	abs.	%	abs.	%	abs.	%
Trihomonas vaginalis	15	13,6	12	14,0	7	12,9	-	-
Candida albicans	64	58,2	57	66,3	36	66,7	5	16,7
Gardnerella vaginalis	53	48,2	44	51,2	38	70,4	6	20,0
Lactobacterium	17	15,5	9	10,5	8	14,8	23	76,7
Chlamydia trachomatis	49	44,5	32	37,2	25	46,3	2	6,6
Mycoplasma genitalium	14	12,7	11	12,8	9	16,7	-	-
Ureaplasma urealyticum	12	10,9	10	11,6	7	12,9	-	-
HPV	62	56,4	53	61,2	42	77,7	-	-
Herpes Simplex Virus II	32	29,1	28	32,6	19	35,2	-	-
CMV	6	5,5	7	8,1	2	3,7	-	-

Microbiological studies data analysis showed that in 157 (62,8%) of women there was identified DNA of HPV. We determined the presence of DNA of HPV in 62 female patients (56,4%) with CIN-I, in 53 women (61,2%) – with CIN-II, and in 42 women (77,7%) – with CIN-III. HPV detection rate increases with the increase of severity of neoplastic process under CIN-II in 1,1 times as compared with CIN-I, under CIN-III in 1,4 times and 1,3 times respectively to the indices of CIN-I and CIN-II.

Analyzing the data of HPV quantification, we found out three variants of viral load (copies of Ig HPV/10^5 cells) (table 2.). In 52 women (33,1%) we detected HPV with viral load <3 copies of Ig HPV/10^5 cells, 3-5 copies of Ig HPV/10^5 cells were detected in 65 female patients (41,4%), and in 40 surveyed patients (25,5%) was detected viral load >5 copies of Ig HPV/10^5 cells.

Table 2: The viral load of HPV in the examined patients (abs. nmb., %).

Copies of Ig HPV/10^5 cells	Groups under study						Total (n=250)	
	CIN-I (n=110)		CIN-II (n=86)		CIN-III (n=54)			
	абс.	%	абс.	%	абс.	%	абс.	%
<3	22	35,5	17	32,1	13	30,95	52	33,1
3-5	29	46,8	21	39,6	15	35,7	65	41,4
>5	11	17,7	15	28,3	14	33,3	40	25,5
Total	62	56,4	53	61,2	42	77,7	157	62,8

Analysis of the distribution of viral load to CIN severity showed that quantitative value of 3-5 copies of Ig HPV/10^5 cells (41,4%) dominates in three groups: under CIN-I this indicator was observed in 46,8%, under CIN-II – in 39,6% and under CIN-III – in 33.3%.

Insofar there is a belief that herpes simplex virus type 2 potentiates dysplastic process in uterine cervix, especially with HPV, we have analysed its index. While studying genital microbiocenosis in women with CIN associated with papilloma viral infection HPV2 was detected in 22 female patients (14,01%). We traced the interrelation between HPV and HPV2 association and the severity of neoplastic process, so under CIN-I this associative form was observed 11,3% of female patients, under CIN- II – in 15,1%, under CIN-III – in 16,7%.

The dominant infection that accompanies the PVI is a fungal infection (45,9%), the detection of which is the highest under CIN-III (54,8%). Along with human papilloma viral infection in women with CIN is detected sexually transmitted infection, namely Chlamydia trachomatis (25,5%), *Mycoplasma genitalium* (11,5%), *Ureaplasma urealyticum* (8,9%). The species spectrotype of microorganisms found in women with CIN associated with PVI under fertility failure is presented in table 3.

Table 3: The species spectrum of microorganisms found in women with CIN associated with the MBC for disorders of reproductive function (abs. nmb., %).

Microorganisms	Groups under study						Total (n=157)	
	CIN-I (n=62)		CIN-II (n=53)		CIN-III (n=42)			
	абс.	%	абс.	%	абс.	%	абс.	%
Trihomonas vaginalis	5	8,1	4	7,5	2	4,8	11	7,0
Candida albicans	28	45,2	21	39,6	23	54,8	72	45,9
Gardnerella vaginalis	22	35,4	23	43,4	19	45,2	64	40,8
Lactobacterium	4	6,5	2	3,8	2	4,8	8	5,1
Chlamydia trachomatis	11	17,7	17	32,1	12	28,6	40	25,5
Mycoplasma genitalium	6	9,7	5	9,4	7	16,7	18	11,5
Ureaplasma urealyticum	3	4,8	6	11,3	5	11,9	14	8,9
Herpes Simhlex Virus II	7	11,3	8	15,1	7	16,7	22	14,01
CMV	1	1,6	-		-		1	0,6

There are developed new integrated circuits of treatment of uterine cervix of reproductive age on the background of genitals viral infection, one of which is the use of endogenous inducer of IFN kagocel in combination with the integrated ozone therapy. Applying this scheme leads to rapid regression of complaints from female patients, normalization of colposcopy and cytogram, which was to eliminate manifestations of inflammatory process, restore cell composition and epithelize cervical mucosa during a month after treatment [8].

4. Conclusion

Thus, the analysis of microbiocenosis of vagina and cervical canal in surveyed women indicates the presence of opportunistic pathogens, infections spreading sexually transmittable infections and viral contamination of genital organs under CIN in women with fertility failure. We determined microorganisms' species spectrotype, which indicates the presence of deep disorders in microbiocenosis. This gives us the opportunity to assert that in the development of dysplastic cervical processes in surveying female patients an infectious factor is of importance, namely the association of microorganisms with HPV presence of high oncogenic potential with viral load >3 Ig HPV/10^5 cells and allows evaluate infectious factor as one of the significant reasons for failed fertility.

5. References

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