International Journal of
Health Systems and Medical Science

ISSN: 2833-7433
Volume 1 | No 4 | Oct-2022

Diagnosis of Genital Tract Biocenosis by Polymerase Chain Reaction in Women of Reproductive Age Using Separate Contraception Methods, With Thyroid Diseases

N. KH. Rakhmanova[1], Dj. G. Matrizaeva[2], M. Kh. Kattakhodjaeva[3]

[1]Senior Lecturer, PhD, Department of Obstetrics and Gynecology, Urgench Branch of the Tashkent Medical Academy, Urgench, Uzbekistan.
[2]Doctor of Medical Sciences, Docent, Head of the Department of Obstetrics and Gynecology, Urgench Branch of the Tashkent Medical Academy, Urgench, Uzbekistan.
[3]Doctor of Medical Sciences, Professor at the Department of Obstetrics and Gynecology, Tashkent State Dentistry Institute

Abstract: The target of the research is to study dynamically state the microbiocenosis of the genital tract in healthy and thyroid women using various contraceptives. Healthy women enable a normal vaginal microbiocenosis than women with thyroid disease. There is a necessity to take into account of negative influence of the different types of contraception on microbiota of genital system of women with thyroid disease in reproductive age. In this research the method of dynamics of urogenital tract microbiocenosis were investigated using the PCR technique. Consequently, the result showing substantially higher frequency of thyroid illness in healthy women than in women diagnosed with it characterizes the normal condition of vaginal microbiocenosis came out. In addition to the use of various contraceptives by women of reproductive age, the diagnosis of thyroid disease was taken into account of the negative impact on the microflora of the genital tract.

Key words: contraceptives, urogenital system, vaginal microbiocenosis, dysbiosis, 16 packages of femoflor, Polymerase chain reaction (PCR) test

INTRODUCTION

It is obvious that the presence of bifidobacteria ensures the stability of the normal microflora. Since the normal microflora in the vagina is in the form of lactobacilli, which should not be less than 10^6-10^8 cloning unit/ ml, the presence of bifidobacteria maintains the stability of the normal microflora [1, 3, 6]. Normally, lactobacilli release H_2O_2 when the vaginal pH is 3,8-4,5. If the number of lactobacilli diminishes, the pH of the vaginal environment increases to 5-6 (alkaline environment). Therefore, the facultative microflora grows and pathogenic strains develop, resulting in dysbiosis [2, 4, 5]. A rise in the facultative microflora (gardnerellas, candidiasis, anobium, etc.) from 10^3 cloning unit is one of the indicators of dysbiosis developing. In fact, a biofuel is created when Gardrenella and atopobiums multiply. A biomarker is a colony of bacteria that share genetic information with one another, resulting in antibiotic resistance [1, 3, 8].

In this day and age, a unique technology for assessing the microflora of the female urogenital tract has been proposed, which is based on the polymerase chain reaction (PCR) in real-time mode.

This method simplifies and accelerates the process of determining the urogenital tract biocenosis compared to traditional methods [5, 7]. This diagnostic method is the most sensitive and specialized method of today. To implement these methods, Femaflor test kits have been recommended for practice and have been successfully used abroad. Diagnostic criteria for bacterial vaginosis have been developed by analyzing vaginal mucus using the Femoflor-16 test kit [5, 7]. The authors discovered a 10% drop in lactobacilli and a 10% rise in facultative flora representatives. Pursuant to their findings, the Femoflor-16 test has set criteria for 99 % sensitivity and 93 % specificity in confirming the diagnosis of bacterial vaginosis. Less than 10% lactobacilli, more than 1% G / vaginalis / P.bivia / Porphyromonas spp., and/or more than 2% Enbacterium spp., Sheathia / Leptospira / Fusobacterium as well as more than 1% and/or 0.2 percent of A. vagina were included in the proposed criteria by the researchers.

The objective of the research is to dynamically scrutinize the state of microbiocenosis of the genital tract in healthy and thyroid women using various contraceptives.

As a subject of the research, venous blood serum was obtained for biochemical and immunoenzyme studies, cervical canal and vaginal secretion for polymerase chain reaction research, and statistical data for medical and social studies.

Research methods. Researchers employed a variety of techniques, including general clinical, instrumental, ultrasonography, biochemical, microbiological, immunoenzyme, polymerase chain reaction, medical-social, and statistical procedures.

The research's scientific uniqueness is as follows:

- The significance of appropriate means selection, taking into consideration the criteria of medical acceptability, to eliminate anxiety during the counseling process, was determined for the first time in order to increase the duration and effectiveness of the use of various contraceptives among patients with thyroid gland diseases of reproductive age and among healthy women;
- The amount of anxiety and satisfaction experienced by women of reproductive age while taking various forms of contraception were assessed;
- it was determined that the long-term non-use of selected contraceptives and their low effectiveness are due to the fact that women do not have complete information about the side effects of the means;
- changes of vaginal microbiocenosis from normocenosis to clearly anaerobic and mixed dysbiosis during the use of various contraceptives in women with thyroid diseases;
- an algorithm for optimizing the individual selection of various contraceptives and preventing complications was developed based on the determination of medical acceptability criteria specific to categories 1, 2, and 3 in women with thyroid gland diseases.

Material and Methods

Women of reproductive age who lived in the Khorezm area on a permanent basis were included in our study. They were divided into 2 groups of women with healthy and thyroid diseases, and urogenital tract microbiocenosis 16 against the background of the use of three types of contraceptives (intrauterine device (IUD), combined oral contraceptives (COC), injectable contraception and pure progestin contraception (IC, PPC)) by the PCR method, the dynamics were checked at baseline and after 12 months. In evaluating the results obtained, the following classification of biocenosis species were used [Dmitrieva T.T. and Khammual., 2016]:

- absolute normocenosis-normoflora 80-100% (relatively to the overall number of patients), Ureaplasma spp, Mycoplasma spp-less than 104 hectares/ml, Candida spp-103 hectares/ml;

- conditional normocenosis - 80-100% (relatively to the overall number of patients), normoflora, Ureaplasma spp, Mycoplasma spp- more than 104 hectoliters/ml, Candida spp- more than 103 hectoliters/ml;

- relative normocenosis - normoflora 80-100% (relatively to the overall number of patients), Ureaplasma spp, Mycoplasma spp, Candida spp occur at different levels relative to each other;

- moderate imbalance (aerobic, anaerobic or mixed dysbiosis) - normoflora 20-80% (relatively to the overall number of patients), increased number of anaerobes and/or aerobes relative to normal;

- apparent imbalance (aerobic, anaerobic or mixed dysbiosis) - normoflora up to 20%, the number of opportunistic microorganisms up to 80-100% (relatively to the overall number of patients).

Results and discussion

The results showed that the incidence of vaginal microbiocenosis in healthy women depended on the type of contraception (Table 1).

Table 1. Indicators of vaginal microbiocenosis in healthy women using various contraceptives, %

Levels of microbiocenosis state	1a group n=11	1b group n=14	1c group n=9
Absolute normocoenosis	0	21.4±11.0	22.2±13.8
Conditional normocoenosis	9.1±8.7	21.4±11.0	22.2±13.8
Relative normocoenosis	45.4±15.0	14.3±9.3*	44.4±16.6
Moderate imbalance (conditional and relative anaerobic dysbiosis)	9.1±8.7	14.3±9.3	0
Apparent anaerobic dysbiosis	18.2±11.6	14.3±9.3	11.1±10.5
Mixed dysbiosis	18.2±11.6	14.3±9.3	0

Note: * - Conclusive difference relative to group 1a.

According to the research, no absolute normocenosis was detected in women who were using IUD (group 1a), while among patients using COC (group 1b), PPC and IC (group 1c), these values were close to each other (P>0.05) - 21.4 ± 11 versus 22.2 ± 13.8%, respectively.

In practice, similar results were observed for the percentage of conditional normocenosis (P = 0.05).

The occurrence rate of the relative level of normocenosis differed insignificantly from the previously reported parameters. While this rate was 45.4 ± 15.0% in group 1a, a significant difference was detected in group 1b (14.3 ± 9.3%, P < 0.05) and group 1c (33.4 ± 15.7%, P> 0.05). The analysis showed that the presence of contraceptives in the genital tract in women using IUD

prevents the occurance of absolute and conditional normocenosis, as evidenced by the fact that in women using COC and PPC, IC these indicators occur in one out of four women.

It can be recognized that conditional, relative and apparent anaerobic dysbiosis as well as mixed dysbiosis yielded almost identical results. Hence, all indicators occurred in small percentages and did not differ significantly from each other. This means that contraceptives in healthy women, regardless of the type, had no negative effect on the state of the genital microflora. This was explained by the low percentage of dysbiotic symptoms in the vaginal microflora. Additionally, similar studies have been conducted in women diagnosed with thyroid disease. The results obtained are presented in Table 2.

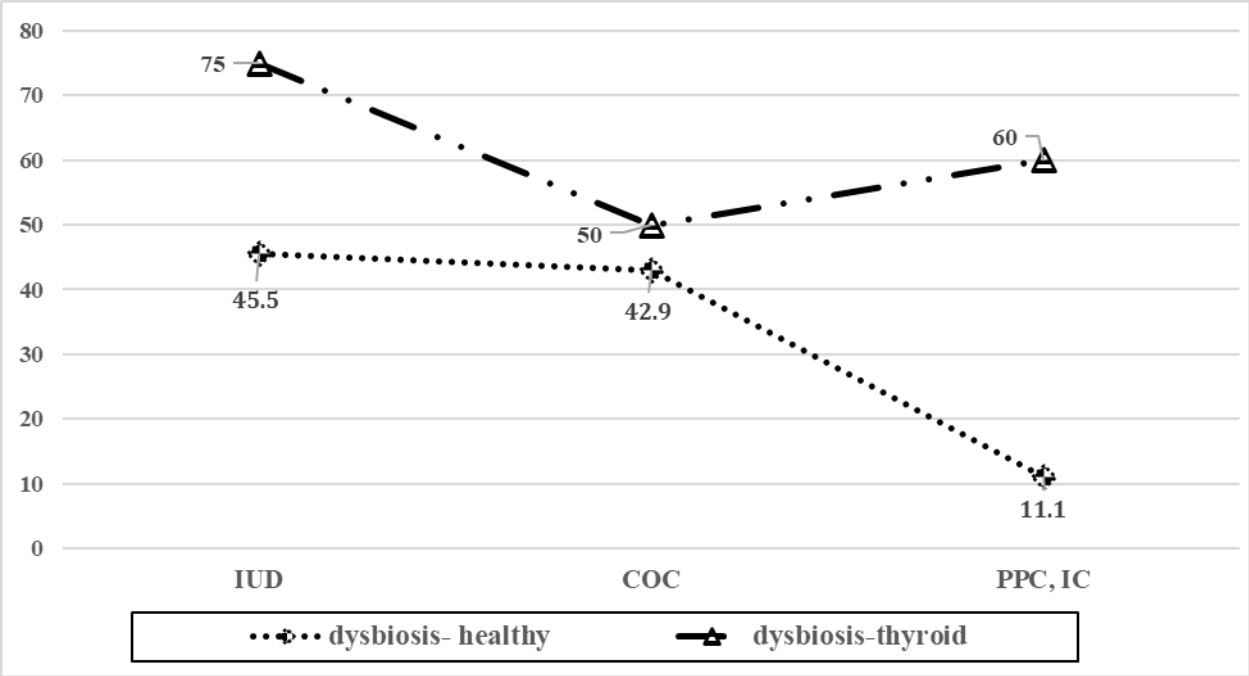
Table 2. Status of vaginal microbiocenosis in women with thyroid disease using various contraceptives

Levels of microbiocenosis state	2a group n=8	2b group n=8	2c group n=10
Absolute normocenosis	0	0	0
Conditional normocenosis	12.5±11.7	12.5±11.7	10.0±9.5
Relative normocenosis	12.5±11.7	0	30.0±14.5
Moderate imbalance (conditional and relative anaerobic dysbiosis)	0	37.5±17.1	30.0±14.5
Apparent anaerobic dysbiosis	25.0±15.3	37.5±17.1	20.0±12.6
Mixed dysbiosis	50.0±17.7	12.5±11.7	10.0±9.5

The results showed that no absolute normocenosis was found, regardless of the type of contraception used. The frequencies of apparent anaerobic and mixed dysbiosis rates were substantially higher in 2a group from the remaining groups. However, when the indicators of all groups were compared with each other, there were no known patterns associated with the microbiocenosis status of different contraceptives.

Eventually, various cases of vaginal dysbiosis in healthy women and women diagnosed with thyroid disease have been analyzed (table 3).

Table 3. The results of vaginal dysbiosis in healthy women and women diagnosed with thyroid disease, %



Ironically, the outcomes were the inverse of the parameters determined by the normal state of vaginal microbiocenosis. To illustrate, the percentage of vaginal dysbiosis was significantly higher in sick women compared to healthy women. The percentage of dysbiosis of studied subgroups were 45.5% and 75.0%, 42.9% and 50.0%, 11.1% and 60.0% respectively. Similarly, the COC parameters were very close to each other. Though, the most remarkable results were detected in women who used PPC and IC.

What is more, according to scientific sources of recent years, one of the most common ways to prevent unwanted pregnancy is hormonal contraception

According to data from the WHO European database "Health for all" (HFA-DB, 2009), 82% of women of childbearing age in France use contraceptives, and 62% of them prefer to use hormonal preparations.

Hormonal contraceptives [79; pp. 66-84, 114; 149-156]:

- combined KV (estrogen and progestin in the form of tablets, injections, sprays, patches);
- non-combined KV (in the form of progestin-preserving injections, tablets, implants, vaginal rings, BIV).

Combined oral contraceptives (COCs) in tablet form contain estrogen and progesterone. Of these, zinnia-f, yarina, janin, diane-35, logest, triquilar, microginon, rigevidon, novinet, regulon, etc. are widely used. COCs are divided into monophasic and polyphasic COCs according to estrogen and progestagen components [36; pp. 36-40, 47; p. 6-7, 89; pp. 27-30, 100; p. 1054-1064, 171; p. 222-228]. COC action mechanism: hypothalamo-pituitary follicle-stimulating hormone (FSG) and luteinizing hormone (LG) levels decrease, ovulation does not occur, ovaries decrease in size, functional aspects of their structure change, proliferative changes occur in the endometrium, cervical hypersecretion and physico-chemical properties of mucus of the cervical canal change. Advantages: highly effective, does not require special examination for use, does not affect sexual intercourse, has non-contraceptive properties, reduces menstrual bleeding, reduces pain during menstruation, prevents anemia, prevents ovarian and endometrial tumors, prevents ectopic pregnancy and genital inflammatory diseases.

Indications: lactating women 6 months after childbirth, women after abortion, women with anemia, women with dysmenorrhea, women with menstrual cycle disorders, women with a history of ectopic pregnancy. Symptoms: thromboembolic diseases, damage to the vascular system of the brain, malignant tumors of the reproductive system and mammary glands, severe disorders of liver function [22; p. 107-110, 36; pp. 36-40, 66; 4-13 b]. Side effects: nausea, headache, dizziness, tremors, hypertension, thrombophlebitis, increased appetite, depression, rapid fatigue, neurodermatitis, skin itching, weight gain, breast enlargement, hardening, jaundice, vaginal candidiasis.

Uncombined KV (IK) in injection form. The first dose of Depo-provera-150 is given on the first five days of the menstrual cycle. Subsequent injections are given every 12 weeks. Noresterate is administered 1 time every 8 weeks, gently mixing the vial and injecting into the deep muscle. IK mechanism of action: stopping ovulation (inhibits the hypothalamo-pituitary system), changes in the physico-chemical properties of the mucous membrane of the cervical canal, enzyme imbalance, changes against endometrial implantation.

Advantages: fast-acting, not related to sexual intercourse, convenient to use during lactation, pain during menstruation is reduced, blood volume during menstruation is reduced, anemia, mammary gland and endometrial tumors are prevented, genital inflammatory diseases are prevented, it is not necessary to always have a reserve.

Indication: when other hormonal drugs cannot be taken regularly, late reproductive age, when there is an indication against estrogens, lactation period, dysmenorrhea [80; pp. 93-95, 85; pp. 36-44, 91; p. 1-2, 107; p. 279-283]. Symptoms: bleeding from the uterus, low-grade tumors of the reproductive system. Side effects: bloody discharge, acyclic bleeding, pain in the mammary glands, depression, headache, weight gain, and so on.

Klein D.A. et al. [144; p.625-633] found that women who use hormonal contraceptives are less susceptible to the development of osteoporosis in the postmenopausal period, and the risk of uterine and ovarian diseases is also observed to decrease among them.

According to the recommendations of WHO experts [15; pp. 28-37, 16; p. 44-45] hormonal contraception is absolutely contraindicated for pregnant women, women who smoke a lot, cardiovascular diseases, severe forms of diabetes, chronic and severe liver diseases, and women with low-quality tumors of the reproductive system.

IK has the properties of not affecting the female sexual function, preventing hyperplastic processes in the myometrium and endometrium, it is convenient to use them in women of late reproductive age, when endometriosis and neuroendocrine disorders are observed [6; pp. 51-56, 128; r.10-16].

One of the side effects of IK on a woman's body is a change in her menstrual cycle. In some cases, this causes subjective discomfort in women, such as amenorrhea, acyclic bleeding, and acyclic bleeding

When gynecological and somatic diseases are detected, the level of these side effects increases, and they do not disappear against the background of medical treatment of women.

Conclusion

In conclusion, there are some positive and negative points to mention

Positive sides: reliability, simplicity of use compared to other KV, no effect on the sexual partner and sexual intercourse, dose not exceeding the norm, low rate of ectopic pregnancy, positive effect on endometriosis, seborrhea and teenage spots;

Disadvantages: the possibility of errors in the administration scheme, the inability to protect against STDs, the presence of negative interactions with other drugs, the increase in the development of inflammatory diseases of the cervix, the development of the process of cellulite formation, high cost.

The mechanism of action of IK is to ensure prolonged anovulation by suppressing the secretion of pituitary gonadotropins [92; pp. 38-42, 84; pp. 47-52, 150; p. 532-536, 170; r.114-120].

The positive aspects of IK are: reduction of vasomotor syndromes, inflammatory processes of small pelvic organs, reduction of incidence of diseases such as iron deficiency anemia and endometriosis [38; p. 217-219, 67; pp. 21-23, 160; p. 426-430]. In addition, taking IK prevents diseases such as uterine tumors, endometriosis, uterine fibroids.

After stopping the use of IK, menstrual function and reproductive activity are fully restored in women for 6-9 months. Sadikova M.Sh. and others. [74; pp. 97-98, 75; p. 5-9; 78; 102-103] studies showed that side effects developed in one out of every two women taking IK. They are mainly amenorrhea, bloody discharge, acyclic bleeding, and women with gynecological diseases have an increased incidence of side effects and their course is relatively severe. The increase in the incidence of side effects depended on the duration of use. The authors acknowledged that 5 of 45 women receiving IK discontinued the regimen because of increased bleeding and anemia after the second injection. On the 23rd day of the retained menstruation and on the 90th day after the injection, according to the diagnostic scraping of the uterus and endometrial biopsy, it was reported that incomplete differentiation of decidual cells, decreased secretory function and atresia were observed in 25 women due to changes in the pituitary adrenal gland system. IK is convenient in the treatment of intermenstrual separations, and its use is an effective method for women with amenorrhea against the background of IK, increased iron reserves and hemoglobin, and iron deficiency [74; pp. 97-98, 75; pp. 5-9].

In a nutshell: 1. The normative status of vaginal microbiocenosis is significantly higher in healthy women than in women diagnosed with thyroid disease. To clarify, in healthy women using IUD, this parameter was 54.5%, while in sick women it was 25.0%.

2. The normative status of vaginal microbiocenosis in women using COC and PPC, IC is 57.1% and 50.0%; 88.8% and 40.0%, respectively;

3. In addition to the use of various contraceptives by women of reproductive age, the diagnosis of thyroid disease should take into account the negative impact on the microflora of the genital tract. Determination of vaginal microbiocenosis using Femaflor-16 was recommended as a criterion for determining the prospects of contraceptive effectiveness.

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