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# "IMPROVEMENT OF TREATMENT OF ENDOMETRIAL HYPERPLASIA IN PREMENOPAUSE"

**Speciality : 5A510101 "Obstetrics and gynecology"**

**THESIS**

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## Contents

## A list of acronyms

**AURTI**- Acute upper respiratory tract infection

**BSD**-Billary-stone diseases

**B/P**- Blood pressure

**BWI**- Body weight index

**CEH**- Common endometrial hyperplasia

**ChID**-Chronic inflammatory diseases

**COC**- Combined oral contrateptive

**DNA**- Deoxyribonucleic acid

**EH**- Endometrial hyperplasia

**EHP**- Endometrial hyperplasy processes

**EIN**- Endometrial intraepithelial neoplasia

**FSH**-Follicular stimulating hormone

**GCEH**-Glandular cystic endometrial hyperplasia

**GnRH**- Gonadoliberin

**LH**- Luteinized hormone

**LRS "Mirena"**- Levonogesterel-releasing systems

**MC**- Menstrual cycle

**NCD**- Neurocerculatory dystonia

**PMS**- Premenstrual syndrome

**SDS**-Separate diagnostic scratching

**TBAE-** Thermic balloon ablation of endometrium

**U-echo-**Medial uterine echo

**USE-** Ultrasound examination

**WHO-** World health organization

## Introduction

**Actuality.** In endometrial hyperplasia processes (EHP) of gynecological pathology structure is from 5 to 25%, has been actual medico-social problems with high rate of recidives and possibility of malignization [48, p.16]. Beside that perfection of treatment methods, mentioned increasing EHP diseases for the last year, which is connected with increasing the number of women, who suffers from disturbance of metabolism, increase of number of chronic somatic pathology, decrease of immunity, as well as unfavorable environment[38,c.40]. In the row of pathological developing, the actuality of endometrial hyperplastic processes, due to high rate of given pathology composition with other proliferative diseases of reproductive system organs. By given separate research in patients with hyperplasia of endometrium presence of hystermyoma and adenomiosis are diagnosed in 13-63% cases, reaching 73% at the age of premenopause [16,p.173]; proliferative changes in mammary glands in 60-80% cases [28, p.48].

Endometrial hyperplastic processes in perimenopause are more frequent cause the bleeding of the uterus, turns to scratching of the wall of uterine cavity [46,c.26]. By given research, among the patients of premenopausal age with anomaly uterine bleeding of EHP are in 54-62% women [28, p.48]. High rate of benign pathology development of endometrial in menopause is connected, as well as age features of neuroendocrine regulation of reproductive system in this period, which sends for hyperplastic changes of mucous membrane of the uterus. But may have a hormonal therapy, which belongs to the main role of conservative treatment of EHP, limited in women of given age group, mostly with burdened somatic status. It is also important, that considerable number of the patients are refuse of surgical therapy, as the presence of uterus and regular menstrual cycle has more meaning for self-consciousness for more women. By the opinion of Ю.Ю.Елисеев (2003), in that case have the role increasing the fear to loose feminity and youth , and also to lose of sexual attract,

simultaneously in refusing of endometrial hyperplasia recurrence in terms till 2 years are noted in 38-95.9% patients [15, p.259].

Nowadays there is low dosaged COCs and have new regimens of dosages, for decreasing endometrial hyperplasia development and clinical manifestation of PMS.

In connection with,

**The Goal** of the research was improvement of treatment methods of endometrial hyperplastic processes in menopause by clinical and morphological data.

**Objectives:**

1. To study somatic health condition and gynecological diseases in women with endometrial hyperplastic processes in premenopause.
2. To determine frequency of separate morphological versions of endometrial hyperplasia in premenopause.
3. To provide comparative evaluation of clinical efficiency of hormonal treatment of endometrial hyperplasia with no atypia in premenopause.
4. To study presented scheme influence of treatment on endometrial condition in patients of premenopausal age.

**Scientific novelty**. It'll study the therapeutically effect of nonstop COC prescription in typical hyperplasia of endometrium.

**Practical meaning** using COC in nonstop regimen in endometrial hyperplasia processes therapy with no atypia let to reach high effect of treatment of tumoral pathology of mucous membrane of uterus in premenopause.

**Mayor conditions, which can be defend.**

1. Hormonal treatment of hyperplasia with no atypia in women at high efficiency of premenopause, within of high rate of recurrence of endometrial hyperplasia leads the necessity of perfectioning of

introducing the patients and principles optimization of hormonal therapy. Treatment tact EHP is defined by morphological characteristic of hyperplasia, patient's age, additional aims, presence of hyperandgrogenia, metabolic patient's state, associated extragenital pathology and presence of contradiction.

2. Hormonal therapy, prescribed in EHP, presents as anti-recurrence therapy, lined on menstrual cycle (MC) correction, releasing non closed estrogenic influence and prevention forming of emdometrial hyrperplasia. The appointment of COC, especially of later generation, assures not only about their high medicinal efficiency, but also additional effects. Coming out from the main task in prophylactic process of endometrial hyperplasia recurrences of hormonal treatment should be directed to decreasing estrogenic function of ovaries. This task is fulfilled at the frame of prolonged regimen usage, connected with more foliculogenesis.
3. Clinical and morphological evaluation of COC Midiana efficiency in non stop regimen for recurrence prophylaxis of EHP in patients at premenopause showed therapeutic effect achievement in 82.1% and warning the clinical recurrence. Morphological recurrence had place in 3.6% cases.

**Introduction:** Has introduced in practice of gynecological department of №2 Maternity complex and Samarkand Regional Multiprofield Medical Center the results of the research. By the theme of thesis has published 7 works and has written methodical recommendations for physicians.

# Chapter I

## Hyperplastic processes of endometrium and modern methods of its treatment

### 1.1. Classification of hyperplastic processes of endometrium.

Endometrial hyperplasia is a vital, complex and multi-faceted problem of practical gynecology. This is due to the fact that this pathology is related to the proliferative processes and without treatment in prolonged duration, it can be a ground for the development of endometrial cancer.

Endometrial hyperplasia (EHP) is the most common form of mucous membrane pathology of the uterus and it is tracked as a non-physiological endometrial proliferation, accompanied by restructuring of glandular and, to lesser degree stromal components of the tissue.

Mechanisms of endometrial hyperplastic processes are not well understood yet, which complicates development of pathogenically substantiated treatment system for patients with this pathology [48, p.16]. Moreover, there is no single generally accepted classification of endometrium hyperplastic changes, which inhibits clear understanding of the process and results in disagreement between clinicians and morphology [27, p.42].

According to histological classification of female genital tract's tumors, which was elaborated by a group of WHO experts [27, p.42] and published in 1975, three types of hyperplastic endometrium were identified: endometrial polyp, endometrial hyperplasia and atypical endometrial hyperplasia.

At the present time, classification which was offered in 1994 by International Society of Gynecologists pathologists and WHO is considered to be more accurate in reflecting structural and cytological changes of endometrium [27, p.42]. According to this classification, endometrial hyperplasia is divided into typical and atypical, which includes not only

structural changes of glands, but also cellular and nuclear atypia. Depending on intensity of structural tissue disorders, each of these groups includes simple and complex hyperplasia.

Some authors use the concept of endometrial intraepithelial neoplasia based on molecular genetics, morphometric and clinical data, including to this group atypical hyperplasia and in situ carcinoma of the endometrium [91, p.26]. In domestic literature there are many terms that characterize atypical endometrial hyperplasia, namely “adenomatosis”, "adenomatous hyperplasia", "cystic adenomatous hyperplasia", "complex adenomatous hyperplasia" and others. However, Н.М.Хмельницкая with co-authors (2006) [27, p.42] believe that these terms do not have analogues in the world literature and considered to be the errors of translation. Thus, the term «adenomatous» should be interpreted as "glandular". Consequently, according to the authors, the term typical complex hyperplasia is synonymous to glandular hyperplasia without atypia and atypical complex hyperplasia –to glandular hyperplasia with atypia, which reflects changes in the morphological characteristics of proliferative endometrium.

Due to insufficient informing of WHO classification’s diagnostic criteria, in 1999 Endometrial Collaborative Group has made another attempt to classify EHP differently. An alternative classification based on histological, cytological, morphometric and molecular genetic criteria has been offered. The authors assume that the point is to distinguish between benign EHP with polyclonal changes and endometrial intraepithelial neoplasia (EIN) - precancerous lesions of the endometrium. Diagnostic criteria of EIN is a monoclonal growth of endometria, center lesion greater than 1 mm and more than 10 glands, specific fraction of stroma less than 55% and expressed cytological changes [53,p.329].

### 1.2. Reasons for the development of endometrial hyperplasia.

In the structure of gynecological pathology EHP occur with a frequency of 15-40% [38, p.40]. EHP frequency varies depending on its form and the age

of women from 10 to 30% [11, p.188]. Most frequently EHP is detected in women between 45-55 years [28, p.48]. According to some authors, EHP occurs in 50% of patients who are in the late reproductive and perimenopausal period [38, p.40].

Risk factors of EHP include early menarche, late menopause, no childbirth, obesity, hyperlipidemia, non-insulin dependent diabetes, menstrual disorders caused by anovulation, endocrine infertility, polycystic ovary syndrome, estrogen – secreting ovarian tumors, hormone replacement therapy in postmenopause [47, p.31].

According to general point of view, the leading role in the development of EHP belongs to excessive estrogenic stimulation, combined with lack of progesterone effect. Although there are new facts that lie beyond this point, the estrogenic concept, however, still remains in the leading role [47, p.31]. Thus, emergence of endometrial hyperplasia may be caused by chronic anovulation of various etiologies, leading to the development of absolute or relative hyperestrogenism [11, p.188].

In addition, excessive proliferation of endometrial hyperplastic processes result in the ovaries, incorrect usage of estrogen, hyperplasia of adrenal cortex, as well as changes in the metabolism of hormones because of obesity, diseases of the liver and thyroid [17, p.175]. The endometrium is a hormone-dependent structure which has ability not only to the cyclic updating of almost all cellular composition, but also to a specific response to all changes in hormonal status of the whole organism [28, p.48]. It has been determined that EHP is much more common in women with metabolic syndrome, which includes, among other exchange disorders, also obesity, impaired glucose tolerance, dyslipidemia and hypertension [38, p.40]. However, according to some authors, development of hyperplastic processes and endometrial cancer does not always occur against hyperestrogenemia [47, p.31]. In a study conducted by О.В.Шарапова and co-authors (2006), [47, p.31] serum estradiol level in patients with EHP was 25%

lower than in women without endometrial disease, generally corresponding to the accepted norm. Based on obtained data, the authors conclude that the increase in the concentration of estradiol is not a necessary condition for the formation of endometrial hyperplasia and therefore, there are other mechanisms underlying the pathogenesis of this disease.

Almost all authors are similar in opinion that changes in the hormonal relationship play a role in the development of proliferative processes in the endometrium. The endometrium as "target tissue", is influenced by sex hormones, and appears to be extremely sensitive to estrogen effect, which influences on its structure and function. Estrogen is the main factor causing proliferation of the endometrium, which in the absence of sufficient progesterone influence, progresses in the glandular and atypical hyperplasia.

Destruction in relationship between progesterone and estrogen and occurrence of relative hyperestrogenemia is caused by anovulation. According to modern concepts, the hormones do not cause neoplastic cell transformation directly [42, p.59]. At the same time, they create conditions under which the risk of cancer under the influence of true carcinogens increases. There are three of these conditions: an increase in the pool of proliferating cells, weakening of anti-tumor immunity, and reduced ability to repair DNA.

In many patients, the EHP is not an independent disease, but a morphological marker of hyperestrogenia, as a result of a benign tumor, or primary ovarian cancer [42, p.59]. However, data from studies on possibility of the EHP in the absence of hormonal disorders, indicates the presence of other mechanisms relating to endometrial hyperplasia associated with a local destruction in regulating cell proliferation and local changes in tissue metabolism [45, p.64]. Besides estrogens, there are other activators of endometrial proliferative activity, namely growth factors and proliferation markers that are necessary for replication of genomic DNA [61, p.32].

In addition to systemic changes, great importance in the formation of EHP is played by proper endometrial response to provided hormonal effects. The literature extensively discusses the role of hormonal-receptoral interactions in the development of the EHP, which are modulated by specific cytoplasmic and nuclear receptors. These irregularities in the EHP may be associated with a deficit of progesterone receptor in the cellular elements of the corpus uteri [65, p.1632].

It is believed that the EHP may be genetically determined [61, p.32]. One of the important parts of EHP etiopathogenesis is chronic endometritis [3, p.167]. In chronic endometritis there is not only increased proliferation of endometrial cells, but also apoptosis, and the balance between the processes is supported by tissue homeostasis. The development of abnormal endometrial proliferation or atrophy in chronic endometritis is possible by distraction of balance between the different processes of proliferation and apoptosis (especially against viral infection) [3, p.167].

## 1.3. Modern methods of treatment of endometrial hyperplastic processes (EHP) in premenopausal period.

Currently, health, quality of life and overall life prognosis in women during perimenopause is determined primarily by adequate and modern treatment - preventive measures, where hormone therapy plays an important role [71, p.54].

Literature analysis shows that a variety of methods and approaches to curing EHP is used today, namely, removal of pathologically altered endometrium, hormone therapy and surgery. However, no single generally accepted classification of the EHP prevents a clear understanding of disease process and often leads to disagreements between clinicians and morphology, which is reflected in the choice of patients' tactics with EHP [84, p.790]. Clearly, the development of endometrial hyperplasia comprises numerous

factors, which contribution in forecasting beginning of disease and progression of disease process to the clinician is difficult to estimate, but this complicates objectification of selecting management of patients. One of the most significant factors, which are directly linked with the risk of developing this disease, is premenopausal period, where prerequisites for the emergence of hyperplastic processes occur in the reproductive system as a result of appeared hormonal changes. A pathogenetic approach to therapy cannot be offered without knowing exact mechanisms of development process and its genetic conditions. This may explain the lack of common recommendations while choosing the drug, dose and its optimal usage duration, which is often inadequate and therefore there is a high possibility of the EHP relapse. In the presence of EHP, therapeutic tactics are generated after morphological verification of the diagnosis. One of the most common treatments of EHP without atypia is conducting hormone replacement therapy [100, p.365]. According to several studies, the hormonal therapies' efficacy of EHP without atypia is low - 42% [100, p.365]. Due to others, EHP relapses are identified only in 26% of women treated with hormonal therapy [28, p.48]. Prescription of hormonal drugs is preceded by histological examination of the endometrium, obtained in a result of SDS.

Despite many proposed schemes and methods, deficiency of hyperplastic processes' therapy is caused by complexity of structure and functions of the endometrium, as well as its multifactorial regulation. Treatment of the EHP should be gradual, complex, affecting the relevant parts of the reproductive system, as well as differentiated, depending on the patient's age, nature of the pathological process in the endometrium and accompanied pathology [38, p.40]. Medical tactic of EHP is determined by morphological characteristics of hyperplasia, patient's age, additional purposes, the presence of hyperandrogenism, metabolic status of the patient, concomitant extragenital pathology and contraindications [48, p.16]. The main method of therapeutic

intervention in the EHP is a sex steroid therapy, which has a number of limitations for use in women with extragenital pathology.

Hormonal treatment of endometrial hyperplastic processes, revealed by uterine bleed, is carried out for achieving multiple effects that are associated with each other:

1) Stopping the bleed;

2) Termination of abnormal proliferation of the endometrium;

3) Normalization of relations in the hypothalamic - pituitary - ovarian system

Hormonal therapy, prescribed for the EHP, is anti-relapse therapy aimed for correcting the menstrual cycle (MC), eliminating uncovered estrogenic effects and preventing formation of endometrial hyperplasia. Currently, there is a wide range of products for the treatment of the EHP in doctors' arsenal. They include progestin, COC, antigonadotrop drugs, GnRH agonists. The effectiveness of hormone therapy is quite high. According to several authors [72, p.1], relapse of common endometrial hyperplasia (CEH) has been identified in 26% of patients treated with hormone therapy, and 72.1% of women without this therapy. Several groups of drugs are used for the treatment of EHP.

The main method of treating endometrial hyperplasia in perimenopausal period, after evaluation of pathological studies, with concomitant gynecological and somatic diseases, is hormone therapy with the provision of anti-estrogenic effect on the mucous membrane of the uterus, by the help of drugs with progesterone activity - synthetic progestins, "pure" progestins. They are consumed in shortened courses of total 6-12 months' duration. The high frequency of endometrial hyperplasia relapse dictates a need in improving management of patients and optimization of the principles of applying hormone therapy.

Taking into account the crucial role of excessive influence caused by estrogen and progesterone deficiency, the appointment of progestogen, which has progestogenic and anti-estrogenic activity, can be considered as EHP standard therapy. Under the influence of progestin, inhibition of proliferative activity, secretory transformation of the mucous membrane, decidual stromal reaction, and with further use - atrophic changes in the glands and stroma sequentially occur in endometrium [85, p.81]. Progestins (progestogens) may be used in any form of EHP- from CEH without atypia to atypical. Morphological conclusion modifies the choice of progestogen and its mode of conduction. Comparative evaluation of different modes of progestogens' appointment indicates higher efficiency of extended-therapy [46, p.26]. One of the therapeutic effect components of progestogen activity is the induction of apoptosis, which explains pronounced reduction in the glandular system successful treatment [46, p.26]. From the point of endometrial hyperplasia treatment, two most significant effects of progestins are important: secretory transformation of the endometrium and the suppression of ovulation. The use of drugs with progesterone -like action ( Djufaston, LRS "Mirena", Norkolut, Progesterone 1% and so on) is justified by the biological effects of progesterone. Progesterone prevents estrogen-induced cell division and therefore creates conditions, under which proliferative endometrium is converted into the secretory. The essence of biological action of progesterone is manifested in anti-estrogenic effect, which is carried out by two mechanisms: 1 - decrease in the number of cytosolic estradiol receptors by inhibiting their synthesis; 2 - progesterone induces 17B - hydroxysteroiddehydrogenase, which converts estradiol into less active estrone.

But long-term systemic consumption of progestogen, which is required to achieve and maintain a therapeutic effect, is often limited by the emergence or worsening of metabolic disorders.

The main effect of antiprogestins (gestrinone) lies in influencing the hypothalamic-pituitary system - the suppression of the release of gonadotropins and insignificant inhibition of their synthesis [52, p.393].

GnRH agonists are successfully used as monotherapy of EHP. These drugs, acting on the pituitary-ovarian system - the endometrium, cause amenorrhea ("pseudomenopause"), which has temporary and reversible character [16, p.173]. In addition, the drugs have an anti-proliferative effect on endometrial cells by binding with high affinitive specific receptors with gonadotropin-releasing hormone [16, p.173]. However, prolonged use of these drugs is limited, due to their negative impact on the metabolic processes and the quality of life. In recent years more and more people are acquiring treatments with minimum side effects. The long history - more than 50 years - use of COC, especially its latest generation, reflects not only their high therapeutic efficacy, but also other positive effects. It is known that the use of COCs for 12 months reduces the risk of endometrial cancer by 50% [85, p.81]. The same protective effect is equal to the all major histologic subtypes of endometrial cancer and persists for more than 20 years after the abolition and taken to be maximum in women from high-risk group.

Under the influence of COCs, endometrium undergoes rapid regression in the proliferative phase, premature secretory transformation of the glands appears inside it and deciduous transformation is observed in stroma. First of all, processes of regression are related to glandular component, so the relative amount of stroma prevails in a ratio of stromal and glandular components. Endometrial vasculature is subjected to significant changes: there is oppression of the spiral arterioles' development, and instead of them, the extensive network of capillaries form the surface layers of the mucous membrane of the uterine body.

The observed changes in the endometrium arise due to the effect of progestins, members of the COC. Progestogens' component COC has a big

variety. From the point of the treatment of endometrial hyperplasia, special significance is shown by the transforming ability of progestin, a member of the COC. The most potent progestins include: norgestimate, levonorgestrel, desogestrel and gestodene, which represent COC progestin component of II and III generation. Synthetic progestins of III generation - gestodene and desogestrel have less residual androgenic activity, compared with progestins of I and II generation. In addition, having a high bioavailability with minimal androgenic activity, desogestrel and gestodene may be considered as the choice of progestins in the appointment of COCs ( Regulon and Lindinet 30) for patients with the EHP.

A special place among the progestogens is occupied by dienogest with the properties of 19- norsteroids. Pharmacological properties of dienogest are similar to the effect of natural progesterone in many ways (high selectivity for binding to the progesterone receptor, absence of adverse effects on metabolism). Dienogest with pronounced anti-proliferative effect is progestin of choice in the appointment of COCs for the treatment of endometrial hyperplasia.

The estrogenic component of COC is presented by ethinylestradiol. For EHP treatment, low-dose monophasic drugs are used. The most common symptoms of endometrial hyperplasia are abnormal uterine bleedings, and therefore, the task of a good cycle control is put on the same level as the prevention of hyperplastic process' relapse. Usage of low-dose COC compared to micro-dose drugs ensures an adequate cycle. It is optimal to conduct 6-12 cycles of drugs' consumption in the normal way (21-day intake at 7-day intervals). Thus, for the treatment of EHP and regulation of MC, it is advisable to use low-dose monophasic COCs that contain a progestin with expressed anti-proliferative effect.

EHP is apolietiologic disease, not only dishormonal violations, but also infectious and traumatic factors play an important role in its development... In

this regard, the literature widely discusses issues relating to the treatment of chronic endometritis [3, p.167].

Given the high rate of recurrence of the EHP, important questions which include a long-term management programs aimed at preventing recurrence of endometrial hyperplasia and uterine bleeding. On the basis of the main challenges in the prevention of endometrial hyperplasia relapses, hormone treatment should be aimed at reducing estrogen producing ovarian function. Without a doubt, this task is best carried out on the background of extended-COC associated with a more pronounced decline in folliculogenesis. When using this COC mode, there is a sustained reduction in estradiol levels, due to the absence of follicular activity and, consequently, the level of estradiol in the days free from receiving hormones. Persistent decline in estradiol is the key to the therapeutic effectiveness of the method, which covers excess of estrogenic effects.

Now, in addition to the progestogen, estrogen-progestin drugs, for the treatment of endometrial hyperplasia in patients during menopause, anti-gonadotropins are used: danazol - derivatives 17a - etiltestosterona of 400-600 mg. daily, gestrinone or nemestran - derivatives 19 – nor steroids of 2.5 mg. two times per week continuously for 6 months. These drugs have a pronounced antigonadotropic effect, contribute to suppression of ovarian function and, as a consequence, cause hypoplasia and atrophy of the endometrium, the most important in the later period of menopause [16, p.173].

Premenopausal period is characterized by a high rate of concomitant extra-genital pathology in patients with EHP. We found that leading position in the structure of extra-genital morbidity in patients with EHP is occupied by cardiovascular disease, which is mainly represented by arterial hypertension, manifested in the form of essential hypertension (32%) and in the form of neurocirculatory dystonia (NCD) for hypertonic type which was registered in 13% of women with EHP. The presence of hypertension and NCD of

hypertensive type greatly complicates the choice of optimal hormonal therapy for patients with EHP in premenopausal period for preventing relapses. This needs a long-term program for managing patients with EHP in conjunction with concomitant cardiovascular disease, aimed at preventing relapses of endometrial hyperplasia by using COC with anti-mineralocorticoid activity. Hyperplastic processes developed during perimenopause have varying degrees of development, and sometimes obtain the character of precancerous disease. Hyperplasia relapses, together with other genital pathologies require radical surgery [15, p.259]. The indication for surgical treatment of EHP is a recurrent endometrial hyperplasia, which is developed in the background of neuroendocrine diseases (diabetes, obesity), presence of concomitant pelvic pathology (hysteromyoma, adenomyosis, ovarian tumour, cervical diseases), lack of efficacy of hormone treatment, simple and complex endometrial hyperplasia with atypia [15, p.259]. There are two types of EHP surgery - ablation and hysterectomy. Since mid-90s of the twentieth century the method of endometrial thermal balloon ablation (TBAE), which became an alternative to hysteroscopic resection and ablation of endometrium, as well as the hysterectomy. Ablation (removal) of the endometrium includes electric destruction of the endometrium by using electrodes with a broad base and mucosal resection by electric hinges. Laser ablation, microwave and photodynamic therapy are also used [32, p.37]. In resource-limited settings, this technique is not widely used in the available literature, there are a few details about the TBAE method [32, p.37], which can be used successfully with uterine bleeding caused by the EHP. This method prevents the long-term treatment with hormonal drugs that are contraindicated in some extragenital diseases.

Hysterectomy is conducted in the presence of EHP in postmenopausal period. The choice of access (laparotomy, laparoscopy) depends on the presence of concomitant gynecological and extra-genital pathology, as well as the skills of the surgeon [16, p.173].

Thus, the choice of optimal EHP treatment is determined by several factors - the age of the patient, the severity of the pathological process, the presence of concomitant gynecological and extra-genital pathology, possibilities of the hospital.

# Chapter II

## Material and research methods.

### 2.1 Clinical characteristic of examined patients.

At the entrance of performed tasks for 2013-2016 period on the of gynecological department of Samarkand Regional Multiprofield Medical Center was been provided a complex clinical and laboratorial examination and treatment of 30 patients with hyperplastic processes of endometrium in premenopausal period. Criteria in research selection are histological verification diagnosis of endometrial hyperplasia with no atypia.

From the research excepted patients with atypical hyperplasia, cancer of womb carcinoma; malignant of intraepithelial carcinoma of uterine cervix; existing hysteromyoma with submucous position one or more nodes, with centripetal growth , also myomatosis nodes, extending womb more to 10 week of pregnancy; severe somatic pathology.

After getting the results of pathomorphological research of patient with endometrial hyperplastic processes, was prescript hormonal treatment (Midiane COC of not stop regimen). The control group was consist of 30 women premenopausal age, whom were planed to prescribe replacing hormonal therapy. For these patients endometrial biopsy were done for excluding its pathology.

Average age of the main group patients' is 45.5 ± 1.99, the control group is 46.8 ± 1.75, which is testify about comparing examined women's group by age qualify. By analysis heredity of diseases of vascular system were found, that in 4(13.3%) patients of the main group family anamnesis were severe form of hypernotic diseases, ischemic diseases, what is exactly did not have any differences from the date of control group – 5(16.6 %).

Burdened anamnesis of heredity by endocrinal pathology in relatives of the I line relates of examined group patients, more in diabetes, were relieved in 3 (10%), and 3 (10%) in main and control group as well.

Analysis of oncological diseases in relatives of the I and II line of relates in examined with endometrial hyperplastic processes showed, that in 11 (36.7%) examined is diagnosed existing malignance in different localization. In the control group existing oncological diseases in relatives was established in 7(23.3%) patients. Thus malignance of reproductive system observed in mothers and girl patients with hyperlasia of endomentry in 8 (26.7 %) cases, in control group anly in 3 (10%). Dates of oncological pathology structure in patients' relatives of the examined group is shown below in table 1.

**Table 1**

**The structure of family oncological anamnesis in examined women.**

| **Diseases** | **The main group n=30** | | **The control group n=30** | |
|---|---|---|---|---|
| | **Num.** | **%** | **Num.** | **%** |
| **Cancer of uterus body** | **2** | **6,7** | **1** | **3,3** |
| **Cancer of ovaries** | **1** | **3,3** | **-** | **-** |
| **Cancer of mammary glands** | **4** | **13,3** | **2** | **6,7** |
| **Cancer of uterus neck** | **1** | **3,3** | **-** | **-** |
| **Cancer of large intestine** | **-** | **-** | **1** | **3,3** |
| **Stomach cancer** | **1** | **3,3** | **2** | **6,7** |
| **Cancer of liver** | **1** | **3,3** | **-** | **-** |
| **Cancer of larynx** | **1** | **3,3** | **-** | **-** |
| **Cancer of pancreas** | **-** | **-** | **1** | **3,3** |

Among benign gynecological diseases in patients' relatives of main group is hysteromyoma and hyperplastic processes of endometry is noted in 12 (40%) cases, in the control group this showing is 4(13.3%).

During the study the anamnesis of the examined group to allergenic reaction for different type of allergens+ ( more in allergenic for tablets) released in 4 (13.3 %) patients of the main group, and in the control group there are in 3 (10%) observed ones. Acute respiratory viral infection, inflammatory inflectional diseases in childhood and adults had a large number of observed patients with hyperplastic endometrial processes. Data of undergone infectious diseases are presented in table 2.

**Table 2**

**Incidence and character of undergone infectious diseases in examined women.**

| Diseases | The main group n=30 | | The control group n=30 | |
|---|---|---|---|---|
| | Num | % | Num. | % |
| AURTI | 22 | 73,3 | 26 | 86,7 |
| Measles | 8 | 26,7 | 2 | 6,7 |
| Rubella | 11 | 36,7 | 6 | 20 |
| Chicken pox | 29 | 96,7 | 21 | 70 |
| Infectious parotitis | 6 | 20 | 3 | 10 |
| Tonsillitis | 15 | 50 | 5 | 16,7 |
| Scarlet fever | 4 | 13,3 | 2 | 6,7 |
| Pneumonia | 3 | 10 | 1 | 3,3 |
| Whooping cough | 2 | 6,7 | - | - |

During the study of extragenital pathology was revealed a high percentage of chronic elementary tract diseases of different types: in 18 (60%) patients of the main and control groups in 10(30 %) observing table 3. Existing hepatitis A in the anamnesis was noted in 3 (10%) and 4 (13.3 %) observing of both groups as well.

**Table 3**

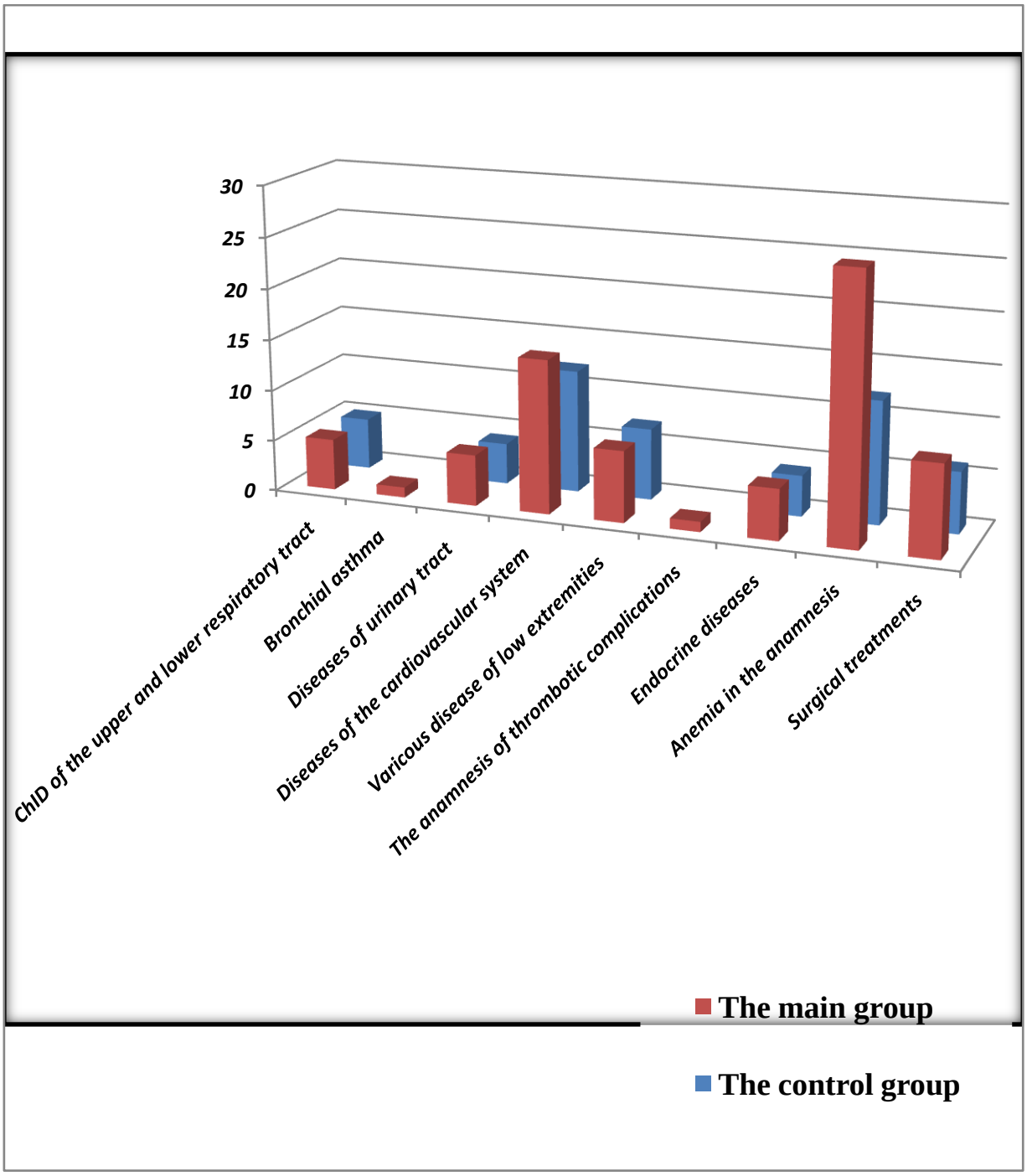
**Incidence and character of elementary tract diseases in examined women.**

| Diseases | The main group n=30 | | The control group n=30 | |
|---|---|---|---|---|
| | Num. | % | Num. | % |
| Chronic gastritis | 7 | 23,3 | 4 | 13,3 |
| Ulcerous gastric disease | 2 | 6,7 | 1 | 3,3 |
| Chronic cholecystitis | 4 | 13,3 | 2 | 6,7 |
| BSD | 2 | 6,7 | 1 | 3,3 |
| Chronic pancreatitis | 2 | 6,7 | 1 | 3,3 |
| Chronic colitis | 1 | 3,3 | 1 | 3,3 |
| Nonspecific ulcerous colitis | - | - | 1 | 3,3 |

Chronic inflammatory diseases of upper and lower respiratory tract predominantly chronic tonsillitis, chronic bronchitis, were revealed in 5 (16.6%) patients of the main group and in 5 (16.6 %) of observed control group (picture 1). Statistically reliable differences were not revealed. With bronchial asthma of mild stage was suffered 1 (3.3%) patient from the main group (pic.1).

In the structure of urinary chanals diseases in women of the examined groups chronic cystitis, pyelonephritis and urine stone diseases were revealed in 16.6% and 13.3% in main and control groups as well ( pic.1). With diseases of cardio vascular system , more hypertonic disease and vegeto- vascular distonia

according to hypertonic type, suffered considerable part of patients with hyperplastic endometrial process -15 (50%) women of the main group, which is reliable didn't increase at control group 12 (40%) (pic. 1).




**Picture 1. The structure of extragenital pathology in examined patients' group.**

Varicous disease of low extremities was found in 7 (23.3%) cases in the main group and in 7 (23.3%) patients of control group (pic.1). Anamnesis of thrombotic complications were burdened in 1 (3%) patient of the main group, while in the control group patients thrombolytic complications were not revealed. By the analysis result of endocrine system-the pathology of thyroid gland, presented as hypothyroidism, nodular goiter and diffuse toxic goiter, were founded in 5 (16.6%) patients of the main group. Nodular goiter in 4 (13.3%) patients of the control group (pic 1). In 9(30%) patient with endometrial hyperplastic process there were surgical treatment of extragenital pathology in the anamnesis: in 5 (16.6%) appendectomy, in 4 (13.3 %) cholecystoectomy, tonsilectomy, resection of thyroid gland in 2 (6.6%) as well. In control group frequency of surgical treatment were 20%: in 2 patients cholecystoectomy and in 4 patients appendectomy.

Thus, patients of both group were compared by age, features of the anamnesis and associates of extragenital pathology.

Mayor attention should be given to the structure and frequency of gynecological diseases in women with hyperplastic process of endometrium. All women of the main group and 83.3% of control group were examined and treated by various gynecological diseases. In their picture 2 you can see, that despite of different number, more in all groups can be observed hystermyoma, endometriosis , ectopia of the uterus neck, fibrous cystic-mastopathy and chronic inflammatory diseases of internal genitals, and less are endometritis, barrenness and tumor of overies. Existing hyperplastic process of endometry of hystermyoma in the patients anamnesis in more percent of cases in 22 ( 73.3%) women of the main group, which for sure was different from the frequency spreading of given pathology in patients of the control group are 9 (30%). the average duration of the disease was similar and consist of $6.3 \pm 5.3$ years in the main group and $6.3 \pm 4.0$ years in women without endometrial diseases. Existing

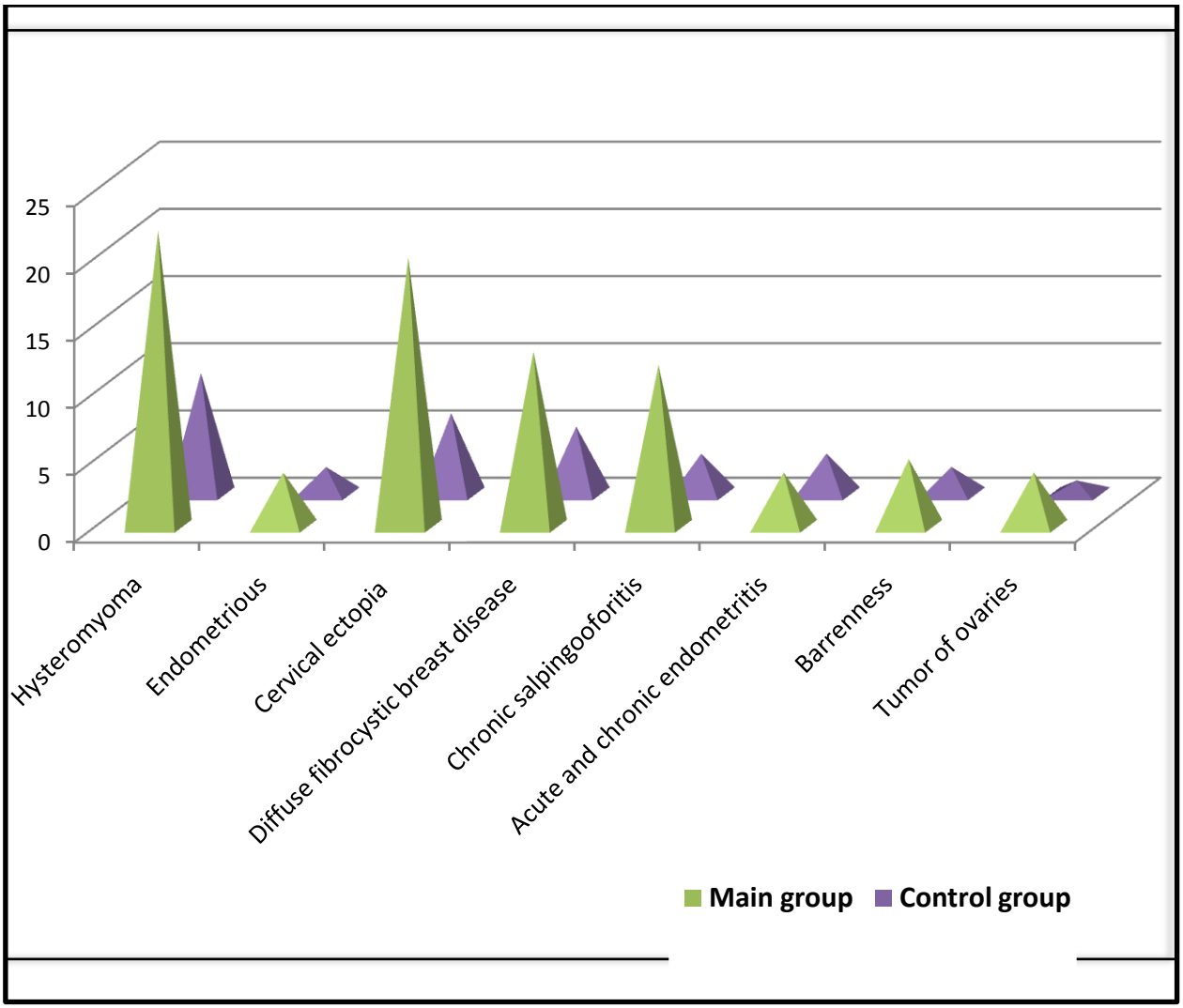
an endometriosis were revealed in the anamnesis of 4 (13.3%) and 2 (6.6%) patients of the main and control group as well.

Ectopia of uterus neck were been in anamnesis in 20 (66.6%) patient of the main group. In 14 (46.7 %) and 2(6.7%) examined patients of the main group were carried out treatment with the surgical diathermy and cryoablation as well. In the same time, ectopy of uterus neck met more less in the anamnesis of the control group than in the main group in 20% cases.

Spreading rate of diffusive fibrous cystic-mastopathy were similar in the main groups in 42.4% and 40.6% women of the I and II group as well. In control group this data were more lower and consist of 16.7%.

Should be noted, that chronic inflammatory diseases of internal genitals were observed exactly in the anamnesis more of the main group, than in control group. Also, the frequency of chronic salpingooforitis among the patients of the main group was 40%, among the patients of the control group was in 10%. Acute and chronic endometritis (by the results of clinic and lab and instrumental examination) was noted in the anamnesis of 4 (13.3%) patients of the main group and in 3 (10%) women of the control group.

Barrenness in the anamnesis was noted in 5 (16.7%) patients of the main group, and in 2 (6.7%) of the control group. Ovaries cancer in the anmnesis was noted in 4 (13.3%) patients of the main group, while in control group was only in 1 (3.3%) woman.

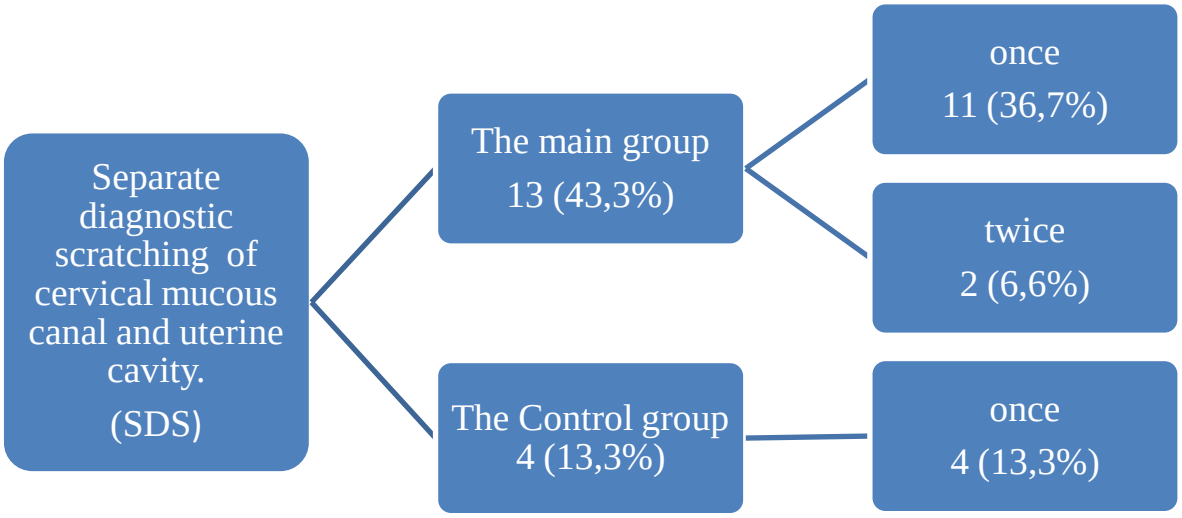



**Picture 2. Structure and frequency of gynecological diseases by given anamnesis of examined women's group**

Should be noted, that in the anamnesis of 13 (43.3%) patients with endometrial hyperplastic processes were done a surgical treatment on gynecological pathology of laporascopy and laporoectomy accesses: reaction of ovary by serious cystoadenoma are in 7 (23.3%) cases, tubectomy for exterauterine pregnancy, sacro and hydrosalpings are in 4 cases (13.3) concentrative myoechtomia and removing paraovarial cysts in 1 case (3.3%) as well. Among surgical treatment, which took place in the control group anamnesis, had an operation, data which were extrauterine pregnancy in 3 (10%); besides, 2 (6.7%) patients were made conservative myoectomia and in

1(3.3%) were removed endometric cysts of both ovaries, coagulation of focal endometriosis.

Separate diagnostic scratching of cervical mucous canal and uteral cavity (SDS) were noted in 13 (43.3%) patients' anamnesis with hyperplastic processes of endometrium, in control group in 4 (13.3%) women. 36.7% and 13.3% patients of the main and control accordingly SDS were carried once; 2 (6.6%) women of the main group were carried the operation twice (pic.3). In the anamnesis of examined control group the repetition of SDS were not noted. Hysteroscopy was not provided not in single patients of the both group, what can tell about diagnostic ability demands in examine of the women in Samarkand Region.




**Picture 3. Frequency of providing separate diagnostic scratching of cervical mucous canal and uterine cavity by the data of examined group women's anamnesis.**

In the anamnesis of the main group patients' the most frequent cystological diagnosis, established in the result of pathomorphological research has gotten of scratching of cervical mucous canal and uterine cavity, was glandular cystic of the endometrium (GCEH) in 56.7% patients from the main group. Besides that, were noted polyp of cervical canal, endometrial polyp and their comparisons, including with GCEH. In control group just in 2 (6.6%) cases were revealed polyp of cervical canal and endometrial polyp as well (table 4).

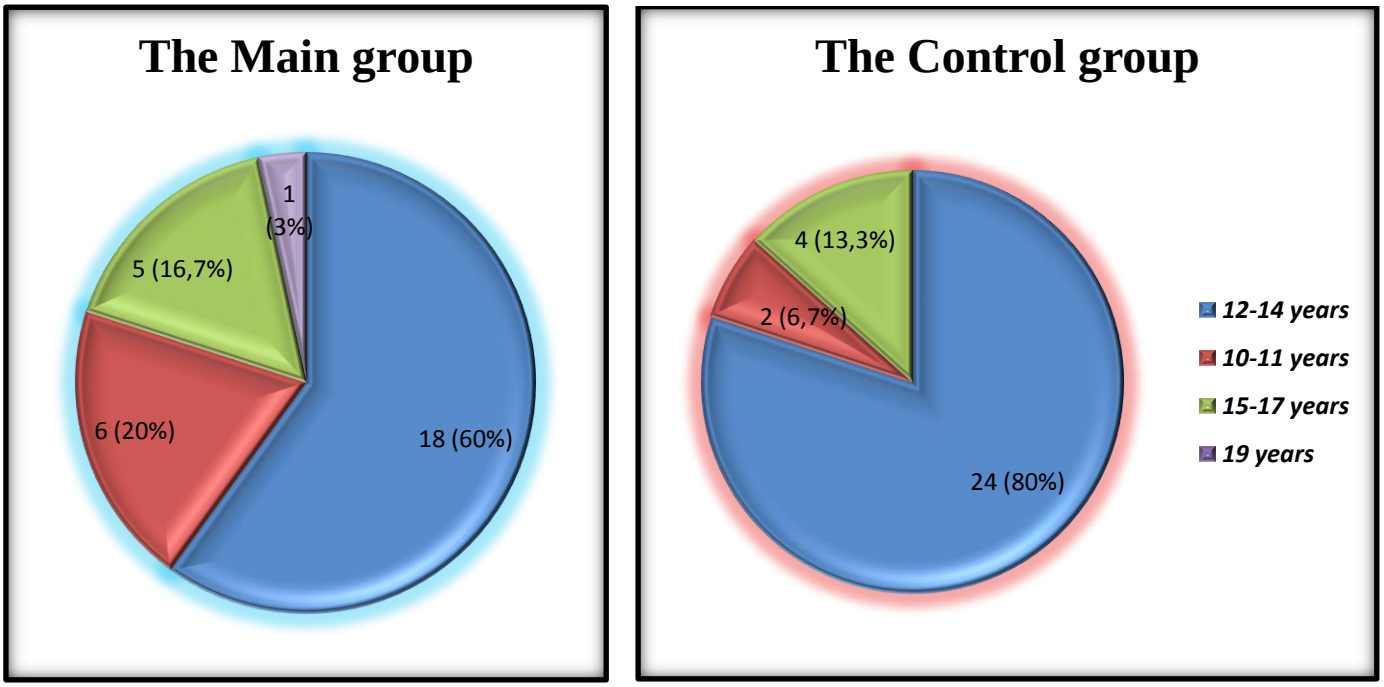
**Table 4**

**Endometrial pathology in the examined patients' group anamnesis**

| Hystological diagnosis | The main group n=30 | | The Control group n=30 | |
|---|---|---|---|---|
| | Num. | % | Num. | % |
| GCEH | 17 | 56,7 | - | - |
| Glandular polyp | 6 | 20 | 1 | 3,3 |
| Fibrous polyp of the cervical canal | 3 | 10 | 1 | 3,3 |
| GCEH and Grandular polyp | 3 | 10 | - | - |
| Fibrous polyp of cervical canal, glandular fibrous polyp of endometrium | 1 | 3,3 | - | - |

Should be noted, that hormonal treatment in the anamnesis got 8 (26.7%) patients of the main group and 3 (10%) women of control group. As hormonal therapy in group took norcolut in 4 cases, dufastone and 17-OPC in 2 cases as well. Should be mentioned , that in all cases of hormonal therapy were stopped by the patients because of bad tolerance of preparations and developing side effects. In control group 2 women had dufastone , and 1 patient had Zhanine.

Were carefully been analyzed being and functioning of reproductive system of examined group women. From the picture 4 you can see, that in most patients (60% and 80% of the main and control group as well) menarche comes on time, at the age of 12-14 years old. Early age of menarche is (10-11 years old) noted more frequently in examined with endometrial hyperplastic processes in 6 (20%) cases, by comparing with control group are in 2 (6.7%) cases; later menarche (at age of 15-17) were revealed in 5 patients with endometrial hyperplastic processes and in 4 women of the control group. The age of is 19 was noted in1patient of I group.




**Picture 4. Age of examined women's menarche**

Thus, the average age of menarche. In examined once was 12.5 ± 1.70 years in the main group and it differentiated from the average of menarche offensive age in women of control group is 13.4 ± 1.22 years. More patients with endometrial hyperplastic in (90% and 93.3 %) women of control group menarche was established during a year.

Menstrual cycle in 96.7 % patients of the main group and in all women of control group the menarche was regular. By the results of anamnesis was established, that in 3 (10%) patients of the main group was observed episode of menstrual cycle disturbance on oligimenorrhea type and opsomenorrhea; may be it is connected with inflammatory processes of endometry and ovaries, and olso hormonal disturbances.

We have analyzed parity of examined women (table 5). In the anamnesis there were pregnancies in 28-93.3% patients with endometrial hyperplastic processes and in 96.7% women of the control group. Has established, that all patients of the main group were 240 pregnancy women. The average for each woman are 8 pregnancies.

**Table 5**

**The parity of examined women**

| **Number of pregnancy** | **The main group n=30** | | **The control group n=30** | |
|---|---|---|---|---|
| | **Num.** | **%** | **Num.** | **%** |
| **0** | **2** | **6,7** | **1** | **3,3** |
| **1** | **3** | **10** | **3** | **10** |
| **2** | **11** | **36,7** | **4** | **13,3** |
| **3** | **18** | **60** | **7** | **23,3** |
| **4** | **12** | **40** | **13** | **43,3** |
| **5** | **6** | **20** | **1** | **3,3** |
| **6** | **3** | **10** | **-** | |
| **7** | **2** | **6,7** | **1** | **3,3** |
| **8** | **1** | **3,3** | **-** | **-** |
| **9** | **3** | **10** | **-** | **-** |
| **10 and more** | **2** | **6,7** | **-** | **-** |

In examined control groups the parity made 3.3 pregnancies of 96 pregnant women in total. Analysis of pregnancy results in patients with endometrial hyperplastic processes showed presents of exact differences of timely deliveries frequencies and artificial abortion comparing with patients of the control group (table 6). In the main group 36.2% pregnancies completed with urgent deliveries, in control group is 46.9 %. Average of artificial abortions were 133 cases in the main group, among the patients of control group were 44 cases.

**Table 6**

**Pregnancy results of examined group patients**

| Pregnancy results | The main group n=30 | | The control group n=30 | |
|---|---|---|---|---|
| | Num. | % | Num. | % |
| Total pregnancy | 240 | 100 | 96 | 100 |
| Timely deliveries | 87 | 36,2 | 45 | 46,9 |
| Preterm deliveries | 5 | 20,8 | 1 | 1,04 |
| Antenatal death of fetus | 1 | 0,4 | - | - |
| Spontaneous labors | 10 | 4,2 | 3 | 3,1 |
| Artificial labors | 133 | 55,4 | 44 | 45,8 |
| Extrauterine pregnancy | 3 | 1,2 | 3 | 3,1 |
| Cystic mole | 1 | 0,4 | - | - |

Been provided somatic analysis, gynecological disorders, reproductive functions of examined women with endometrial hyperplastic processes showed, that in whole for patients with endometrial hyperplastic processes is typically:

- hereditical burdened in huperplastic and malignant diseases of reproductive system;

- increased level of somatic pathology with obtained cardio-vascular diseases and diseases of elementary tract;

- high infectious index;

-features of reproductive functions (more early age of menarche by comparing with control group);

-high frequency of combination of EHP with hyperplastic processes of another reproductive system organs.

## 2.2. Research methods

All patients passed clinical and laboratorial exams, includings:

-Check up – the type of bodybuilding, features of distribitio of subcutaneous adipose of cellular tissue, nature of hair. Were measured high and weight of the patients with following estimation of body weight index ( G. Brey index) according to formula BWI= body weight (kg)/ [high ($m^2$)]. Significance of BWI from 20 to 24.9 kg/$m^2$ was estimated as index of normal body weight, from 25 to 29.96 kg/$m^2$- as overweight, 30-39.9 kg/$m^2$ as obesity and more than 40 kg/$m^2$ as sharply marked (morbid) obesity;

-Gynecological check up (character and volume of discharge from genital canals, to defined the condition of external genital organs; vagina, neck of the uterus, position and the volume, morbidity of the uterus, condition of uterine appendages);

-Smear from cervical canal and vagina in the level of purity;

-Smear with ecto and from endocervical for oncocytology;

-Dilated colposcopia

-Clinical blood analysis, biochemical blood analysis, coagulogram

-USE of a small pelvis.

- Research of the folliculostimulating hormone contention, luteinizing hormone, blood serum estradiol and progesteron;

-Separate diagnostic scratching of mucous cervical canal and wall of uterus cavity;

-Morphological study of curage from uterine cavity.

**Ultrosound examination** to all patient were performed using trans-abdominal and trans-vaginal scanning on " Mylab Class C" with the help of multi-rate switches- transvaginal 5 MHz and transabdominal 3,5-5 MHz. Research been carried till separate diagnostical scraping of mucous cervical canal and cavity of the uterus, after 3 month and after finishing the therapy. With that was evaluated the topography of uterus, its shape, borders and size; difference between a thickness of anterior and posterior walls of myometry, its echogenity and echostructure; the shape of uterus, existing its deformation; endometrium thickning, its shape, echogenity, soundpassage, internal built up and borders' condition; and also size, borders and echostructure of ovaries.

**Research of hormonal profile** was carried out at the diagnostic Center Bionur. For the research took a venous blood of the patients on an empty stomach. Content of the blood serum of luteinizing, follicle stimulating hormones and estradiol were determined on 4-7th day, progesterone on 21st day of menstrual cycle before prescribing therapy. Research was carried by means of radio immunological methods (immune fermental analysis) with the help of commercial machines "DRG" (Germany) on radioimmune analisator "Bio-Chron" (Germany) in all group of patients.

**Morphological research** has carried out at lab of Regional Multiprofile Medical Center. By scraping got an endometrial tissue, tissue was fixed in 10% neutral phormaline solid. After whelming in paraffin made cuts of 5-6 mkm thickness and hemotoxilinum and eosinum. Pathomorphological diagnosis was established on the criteria base, recommended by WHO (World Health

Organization) .Given research of endometry was provided before starting the treatment and after the finishing the course of therapy in order to evaluate its efficacy.

## 2.3 Treatment methods

After the results of pathomophological research of endometry check up for the patients of the main group were prescribed Midiane in prolonged regimen as hormonal therapy with no 7 day break ups for 6 month. Midiana is monophase peroral contraceptive. There are 21 tablets in the box, containing ethinylestradiol in 30 mkg. and drospyrenone 3 mg.

# Chapter III

## Clinical and morphological features of patients condition with endometrial hyperplastic processes and effective estimation of hormonal therapy.

### 3.1. Data of objective examination of studied patients groups

Patients with endometrial hyperplasia addressed to of gynecological department of Samarkand Regional Multiprofield Medical Center with complains for bloody discharge from genital tracts or bleeding.

By the complains results of the patient of the main group was estimated, that in existence of bloody discharge of different intensity were marked in 24 (80%) women. Duration of bloody discharge existence until coming inpatient were 12.6 ± 3.6 days. Besides that, as shown in the 7 table, patients made complains for disturbance of menstrual cycle, pain in the lower side of the abdomen, vasomotor and emotional-vegetative symptoms of in different conditions. Has been determined that patient with endometrial hyperplastic processes is releablly more often than in women of control work, made complains for menorrhargia in 56.6% and for metrorrhargia in 434% cases, and also the existence of pain syndrome is 36.6%, per or post menstrual bloody discharge in 26.6%. in the control group given complains were noted for 2-4 times less. Should be noted, that complain for disturbance of menstrual cycle with the olygometrial type more presented for the patient of the control group in 12 (40%) cases, than in women of the main group 4(13.3%). beside that the is complains for amenorrhea not mentioned among examined with endometrial hyperplastic processes, while each 10th women of control group made such complain.

Has revealed releable difference in the rate of vasomotor occurance and emotional- vegetative symptoms climacteric syndrome in patients of examined groups. Also complains hot flash, sweetening, head ache and rapid heart beats were submitted half part of the control group women and anly 2 (6.6%) patients

with endometrial hyperplastic processes. Frequency of emotional-vegetative symptoms occurrence, such as irritableness, weakness, sleepiness, anxiety, inattentiveness and sadness, was authentic lower in the main group for 10%, by comparing with control group for 70% (table 7).

**Table 7**

**Patients complains while receive.**

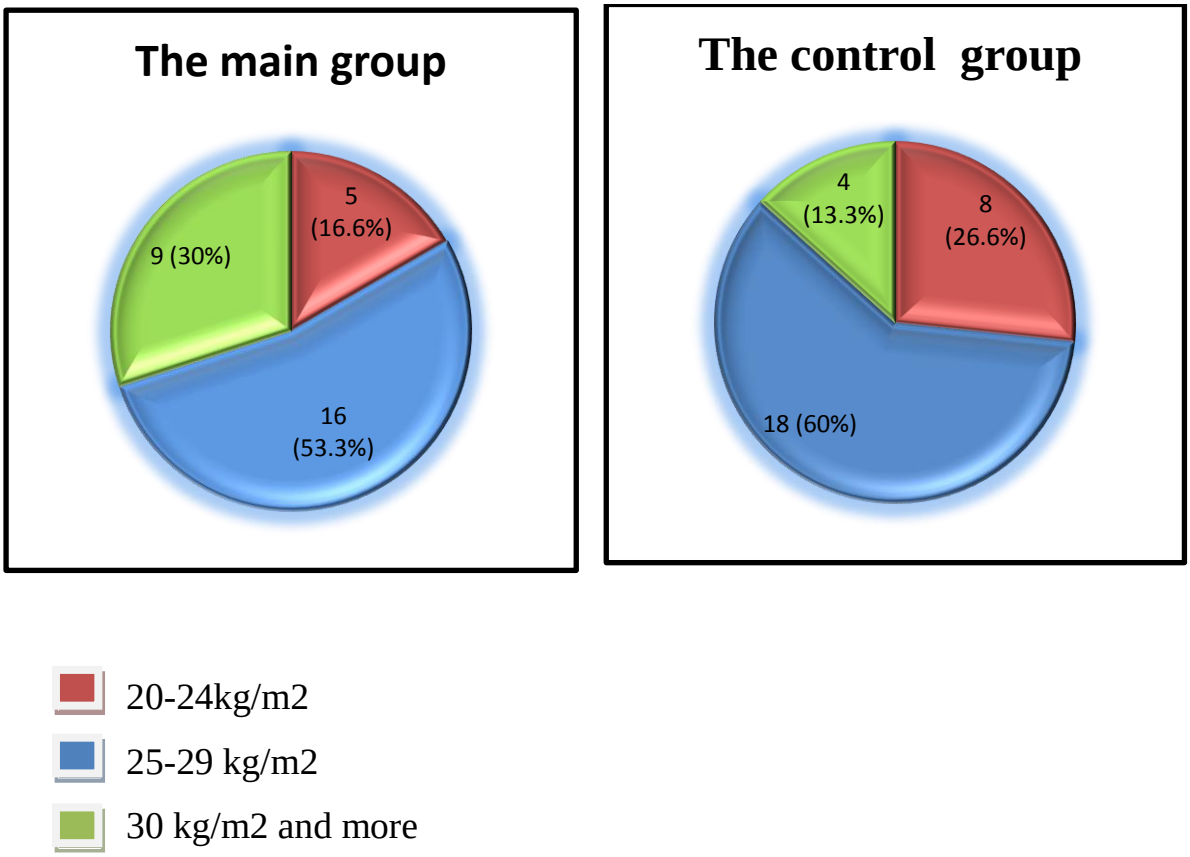
| Complains | The main group | | The control group | |
|---|---|---|---|---|
| | Абс. | % | Абс. | % |
| Menorrhargia | 17 | 56,6 | 8 | 26,6 |
| Metrorrhargia | 13 | 43,3 | 3 | 10 |
| Pain in lower part of the abdomen | 11 | 36,6 | 4 | 13 |
| Pre and post menstrual discharge | 8 | 26,6 | 2 | 6,6 |
| Oligomenrrhea | 4 | 13 | 12 | 40 |
| Amenorrhea | - | - | 3 | 10 |
| Vasomotor and emotional-vegetative symptoms | 2<br>10 | 6,6 | 21 | 70 |

Duration of menstrual cycle disturbance releablely didn't make any differ in all patients and composed for the average 2.5 ± 2.1 years and 2.2 ± 2.4 years in control group.

By the objective check up results were been estimated, that body structure in women's type in all examined patients and secondary genital appearance have developed normal.

Weight and high coefficient ( Brey's BWI) ( body weight index) was according to the normal in 5 (16.6%) examined once with hyperplastic

endometrial processes, in 16 (53.3%) women was constant over weight, in 9 (30%) were obesity. In control group overweight of body mass were noted in 18 (60%) women, obesity were in 4 (13.3%), and the rest 8 patients' (26.6 %) were according to normative (picture 5).




**Picture 5. The amount of body weight index of women in examined group.**

The average value of BWI was 29.23 ± 0.83kg/m in patients of the main group. In control group this date was reliable less in 27.02 ± 0.58 k/g. in the gynecological status research of external genital organs' development are normal in all women. Urethra, paraurethral tracts, large glands ducts of vaginal vestibule with no pathological changes during examination time in all checked up patients. Wall of the vagina is not changed by visual in 78.8% and 66.7% patients of both group accordingly. In 7 patients of the main group and in 5 women of control group was noted descending of vaginal wall.

Pathological changes of uterine neck was found in 16 (53.3%) patients of the main group and only in 7 (23.3%) women of the control group. Among

pathological changes of uterine neck in patients with endometrial hyperplastic processes were find echtopia in 16.6%, hypertrophy in 23.3% and scaring deformation in 13.3% cases.

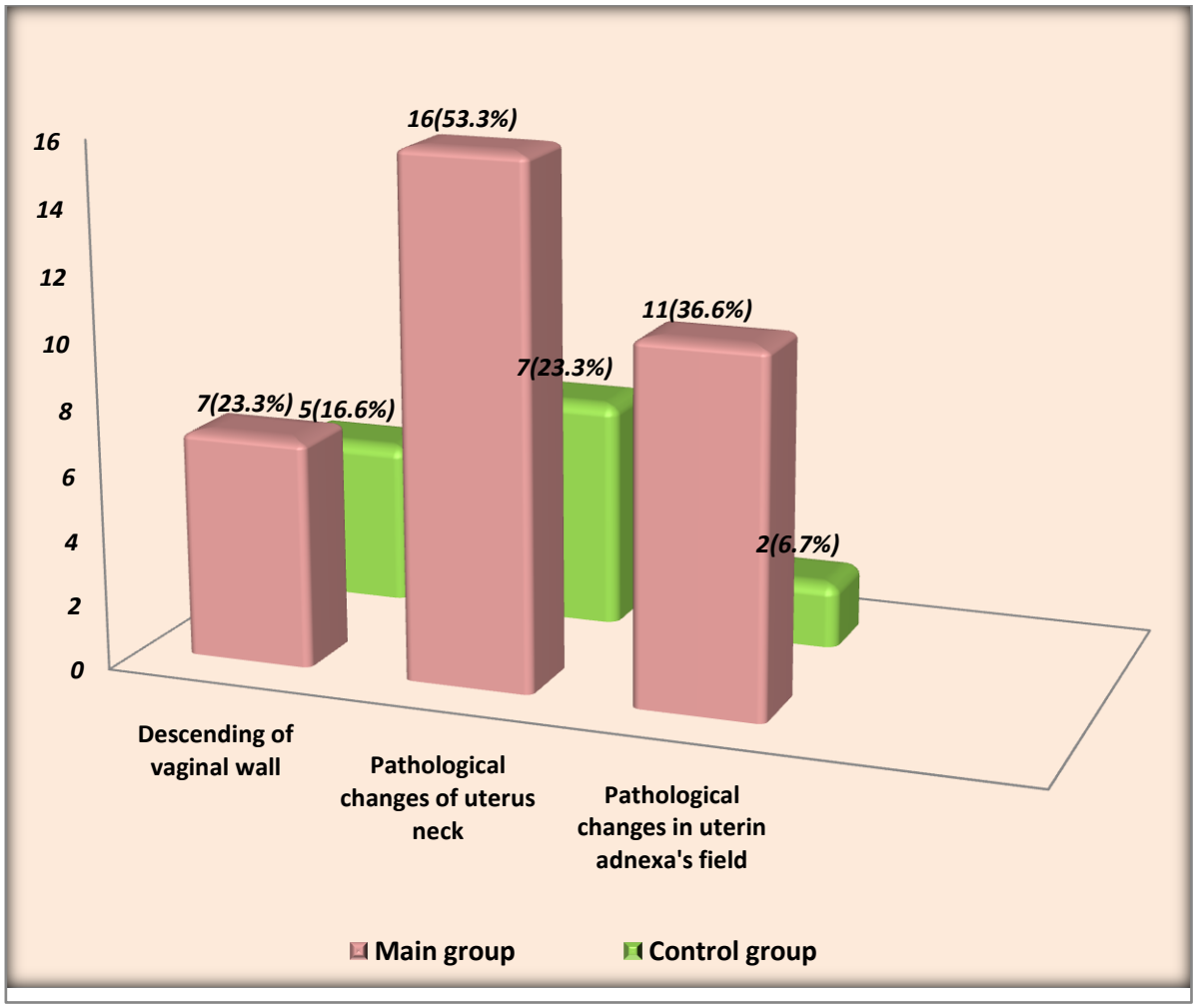
In bimanual research the normal size of the uterus were noted in 6 (20%) patients of the main group, that is reliable noted in comparison with control group in 12 (40%) cases. The size of the uterus, founded by gynecological check up of the examined patients group, presented on the table 8.

**Table 8**

**Uterus size by bi- manual data of examined patients**

| The size of uterus, according to pregnancy term | The main group | | The control group | |
|---|---|---|---|---|
| | num | % | num. | % |
| Normal sizes | 6 | 20 | 12 | 40 |
| 5-6 weeks | 15 | 50 | 11 | 36,6 |
| 7-8 weeks | 9 | 30 | 7 | 23,4 |

Pathological changes in the uterine adnexa field (“burden”, sensitivity in palpation), which can defined about undergone inflammatory processes, were noted in 11 (36.6%) patients of the main group and in 2 (6.7%) women of control group (picture 6).




**Picture 6. Gynecological status features in examined groups.**

### 3.2 Ultrasound examinations data of studied patients' group.

Among patients with endometrial hyperplastic processes in 11(36.7%) patients by submitted were noted profusely bloody discharge. These patients were made SDS operation extremely, USE were done after the currage.

Echographic signs of hystermyoma was found in 22 (73.3%) patients of the main group, there were 9(30%) women in the control group (table 9). Mainly character of the tumor were found in 3 (10%) patients and 2 (6.7%) in control group. There were more frequently myomatosis nodles of interstitial localization of the main group patients in 54.5% cases. In control group were found 3 (3.3%) cases of interstitial localization of myomatosis nodles, in 6 (66.6%) of interstitial subserosis localization as well.

USE signs of diffusion form of internal endometriosis-unequal thickness of the uterine wall, presents of nodal points and small cystic structures in myometry, irregularity of endometrial basal layer thickness, appearance of small hypo and anechogenic structures in the basal endometrial layer area, irregularity of mucous membrane and muscular layer of uterus borders, presents of separate areas of increased echogenity in myometry, directly adjoining to uterine cavity revealed in 4 (13.3%) patients of the main group and only in 2 (6.6%) women of control group (table 9).

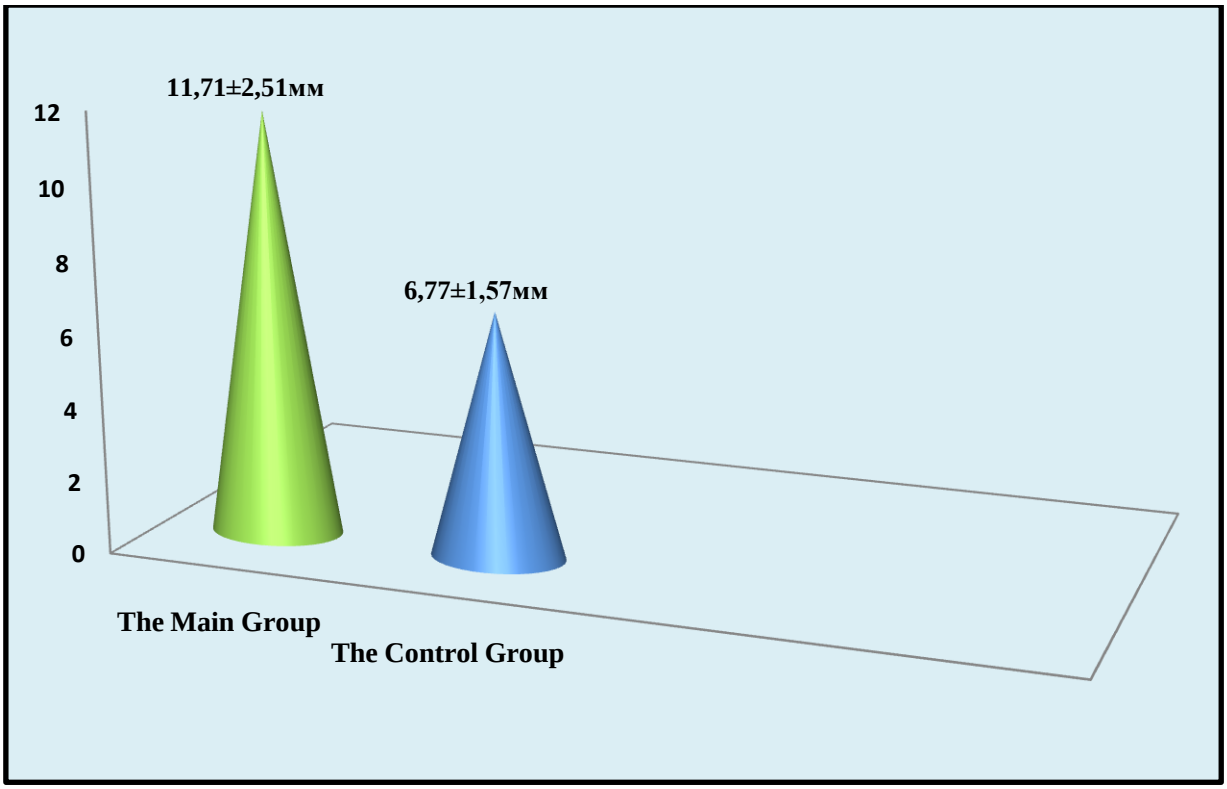
**Table 9**

**Incidence and character of pathological echographic signs in examined women.**

| Revealing of pathological myometry | The main group | | The control group | |
|---|---|---|---|---|
| | Num | % | Num | % |
| Hystermyoma | 22 | 73,3 | 9 | 30 |
| Internal endometriosis | 4 | 13,3 | 2 | 6,6 |
| Combination of myoma and internal endometriosis | 2 | 6,6 | - | |

By US examinations the endometrium of the main group patients , performed before curageing, average thickness of interior and posterior size of medial uterus echo (U- echo) were in the main group 11.71 ± 2.51mm. Echoscopic signs of hyperplastic process of uterine mucous membrane (multifocal structure of endometrium, the presents of echopositive and echo negative inclisions) were revealed in 63.1% patients of the main group.

By the US examinations results, has done in early proliferative phase of menstrual cycle, average extension of U- echo in the control group women is reliable, it was different from given data in the main group and were 6.77± 1.57mm (picture 7).




**Picture 7. Average of U-echo significance in patients of the examined group.**

There were not revealed an echographic signs of pathological changes of the ovaries in examined patients.

### 3.3 Hormonal status of the studied patients group.

Taking into account given literature about important role of hormonal disbalance in the genethis of EHP [42, p.59], we conduct a comparative assessment of patients' hormonal status with of endometrium and women of the control group. Research results of hormonal level of blood serum, are presented in table 10, reliably differentiated in patients of the main group in comparison with the control group.

**Table 10**

**Gormonal contents of blood serum in examined women.**

| Hormone | Measurement units | The main group | The control group |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **LH** | **IU/L** | **9,76±0,61** | **7,13±0,38** |
| **FSH** | **IU/L** | **15,86±0,75** | **33,78±1,56** |
| **LH/FSH** | | **0,67±0,06** | **0,22±0,02** |
| **Estradiol** | **Nmol/l** | **263,04±13,15** | **83,72±3,84** |
| **Progesterone** | **Nmol/l** | **2,25±0,16** | **3,94±0,2** |
| **prolactin** | **IU/L** | **349,1±12,8** | **506,4+11,7** |

Research results of hormonal status in patients with hyperplastic processes of endometrium has established increasing the level of LH, and also ratio of LH/FSH is more than 3 times in comparison with the control group. At the same time, average level of FSH in the main group patients' serum of blood was reliable lower, than in women with no endometrial pathology. Average level of the serum estradiol in patients were correspond with normal data, but reliably differentiated from given data in the control group (83.72 ± 3.84 nmol/l). Progesterone compound in blood serum of the patients with endometrial hyperplastic processes also match with normative data for follicular phase of menstrual cycle. In women of control group the average of the progesterone was reliable higher, than in the main groups, and prolactin contains decreased to 25.1%.

### 3.4. Results of separate diagnostic scratching of cervical canal's mucous membrane and walls of uterine cavity of studied group of patients.

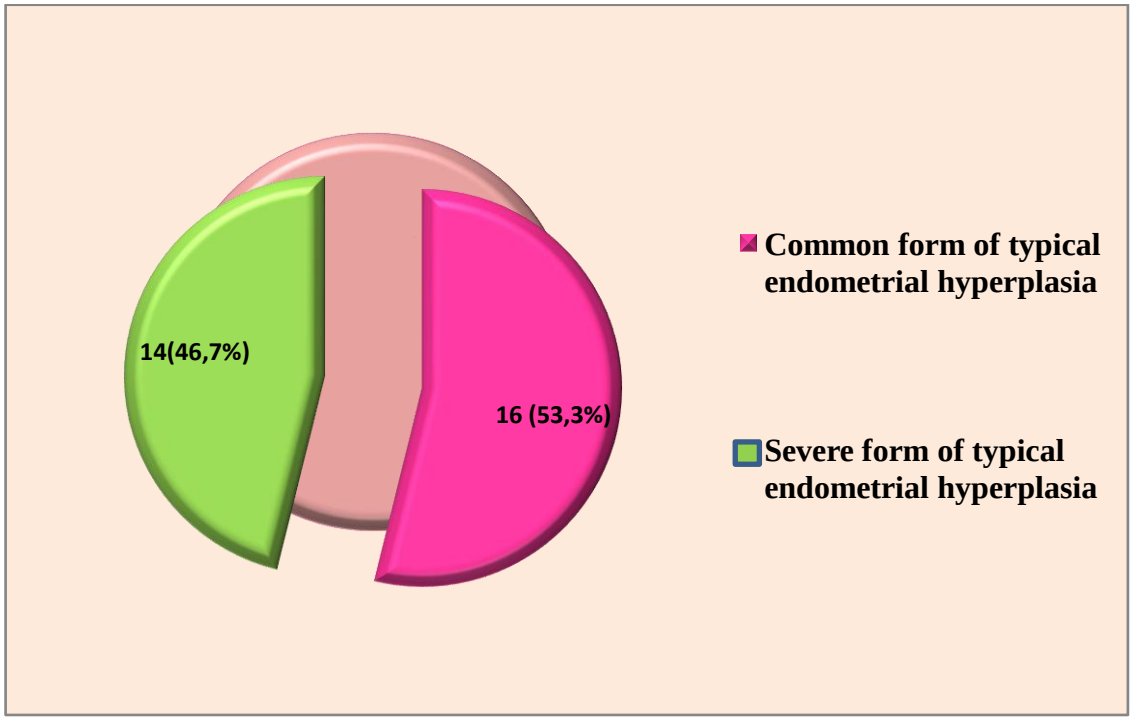
Several diagnostic scratching of mucous cervical canal and walls of uterus cavity were performed to all 30 patients with endometrial hyperplastic processes, 11 (36.7%) patients with profuse bleedy discharges, the operation was made urgently.

In visual evaluation curettages, received from uterus cavity, in 18 (60%) patients curvature interpreted as profuse, in 10 (33.3%) as moderated and in

2(6.7%) as scanty. Rigidity of uterine wall was noted in 16 (53.3%) women. Removed material was sent for morphological research.

There was provided morphological research of endometrium in all researched patients group. In 30 (100%) patients of the main group performed gistological research of curettages from uterine cavity, received during operation of SDS; patients of control group provided a vacuum of endometrial aspiration: in 27 (90%) cases in prolypherative phase of menstrual cycle, in 3 (10%) on amenorea scale.

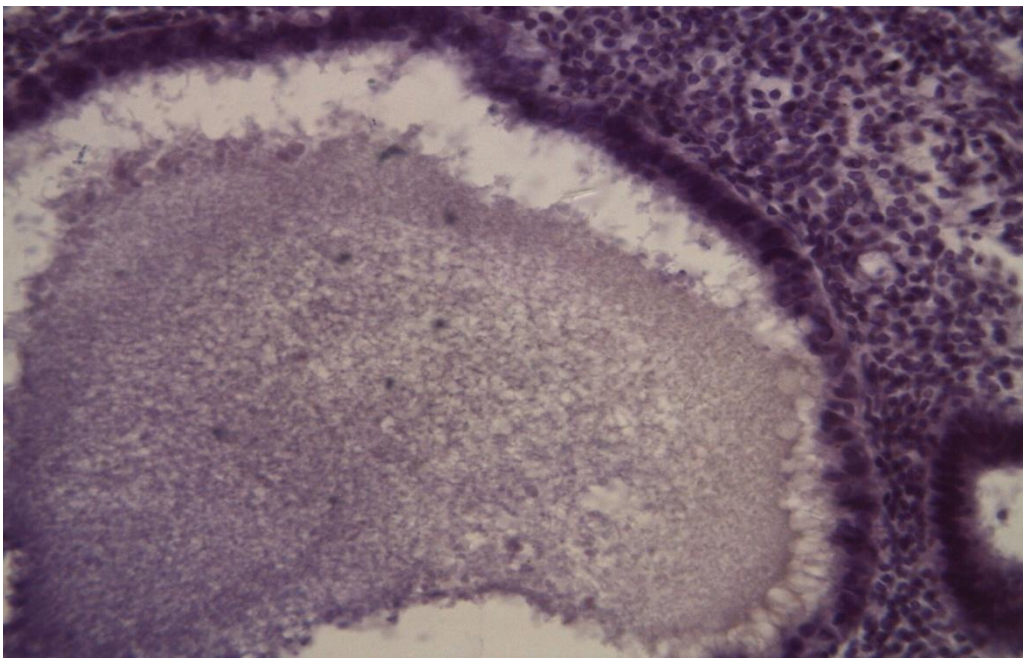
In gistological research of the curvature from uterine cavity, there was revealed endometrial hyperlasia with no atypia, in all cases of the patient of the main group. (picture 8).




**Picture 8. Morphological results of patients' research with endometrial hyperlasia.**

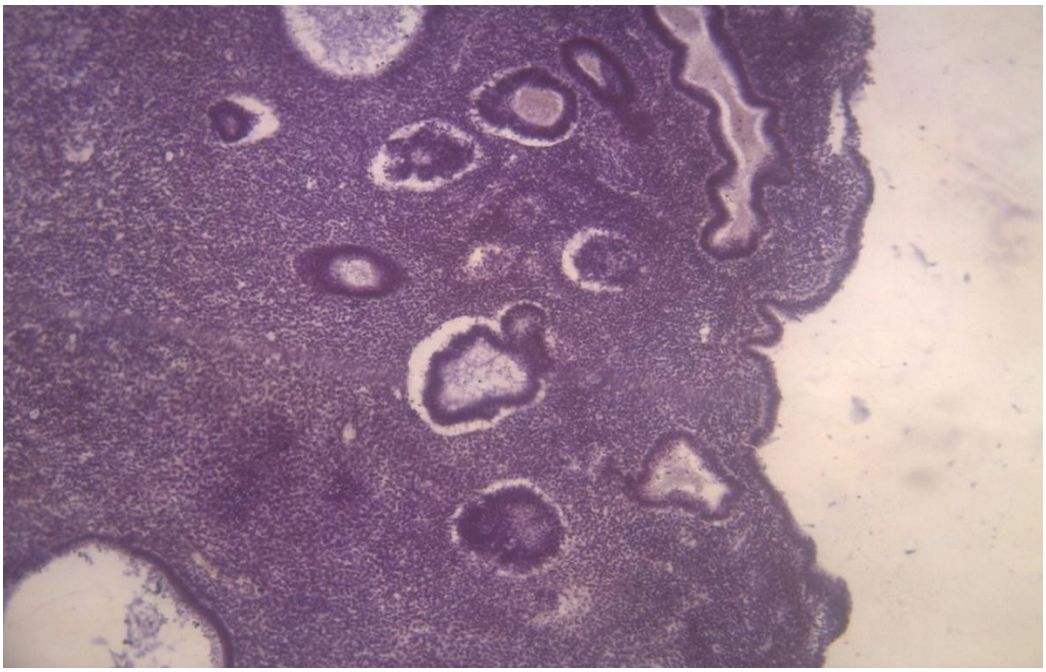
There was found increasing number of as glandular , so and stromal elements in 16 (53.3%) patients by some riches of the first, presents of rounded glands of various on their size, lineded by highly prismatic epithelium with oval

multilinned nucleus situation and straight apical margine; presents a lot of mitosis figures in glandular and also in stromal cells. In the row of the large and small glands, were found cystal deletion of the gland, lined by lowly prismatic epithelium. Given histological data characterized for common form of typical of endometrial hyperplasia. (picture 9).



**Picture 9. Histological signs of common form of typical endometrial hyperplasia.**

There were revealed severe typical endometrial in 14 (46.7%) patients. In the row of increasing a number of glandular elements, morphological picture of endometry of these patients characterized with present of tightly situation of the glands with considerably decreasing a number of stroma among them; increasing structural difficulty of the glands; expressed of multilined epithelium in presence of regularity by the size and form of the nucleolus; considerable number of mytosis fugures. (picture 10).



**Picture 10. Histological signs of severe form of typical endometrial hyperplasia.**

The most frequent histological diagnosis, determined in the result of pathomorphological research of had gotten curvatures of mucous cervical canal and uterine cavity, was glandular- cystic of endometrial hyperplasia (GCEH) in 56.7% patients of the main group. Besides that, were noted cervicalcanal polyp, endometrial polyp and their promtness, with GCEH as well. In the control group only 2 (6.6%) cases was determined cervical canal polyp and endometrial polyp as well.

By morphological examination of mucous membrane of the uterus in women of control group in 28 (93.3%) cases revealed endometrium in polipherative phase, in 2 (6.7%) cases are in secretion phase. Histological picture of 7 (23.3%) cases characterized of presents endometrial signs in early stage of the prolipherative phase.

In histological examination in 21 (70%) women the endometrial surface was lined by highly cylindrical epithelium in absent of functional layer division into zones, appeared glandular structures of winding, spin like form with clearly marked margins of apical margin of epithelium, were noted doublelined, single

mytosis. There were also noted single vessels with thin walls by histological sphere. These signs were correspond with average of secretion phase stage, including clear subdivision of functional layer on spongios and compact layers, presence of strongly developed glandular cript spin like form with fold like lumens and hight secretory activity of epithelial cells, and also developed spiral arteries of function of endometrial layer.

### 3.5 Evaluation of hormonal therapy effect with endometrial hyperplastic processes with no atypia in premenopause.

Hormonal therapy, prescribed in EHP, presents by anti-recurrent therapy, directed to menstrual cycle (MC) correction, reduction of uncovered estrogenic influence and reduction of endometrial hyperplasia formation. In hyperplastic processes the therapy tact is depend on pathomorphological characteristic of endoterium, age, the etiology and pathogenetic diseases, associated genital and estrogenetic pathology.

The major therapy of endometrial hyperplastic processes in the menopause period, after evaluation of pathomorpholigical research, according gynecological and somatic pathology, is hormonotherapy with antiestrogenic influence to mucous membrane of the uterine cavity.

By authors' [72, p.1] data, recurrence of common endometrial hyperplasia (CEH) were revealed in 26% patients, who has taken hormonal therapy, and in 72.1% women, whom this therapy was not carried out.

Prolonged history more than 50 years receiving of COC, especially last generation, presents not only their high medicinal effect, but additional positive effects. It is known that the usage of COC during 12 months decreases endometrial tumor development to 50% [72, p.1]. Protective activity the same to all the minor histological types of endometrial tumor, persists on during 20 and more years after abolition and it is a high risk to women's group. Gystogenic component of COC is different. It has major role in treatment of endometrial

hyperplasia as transforming ability of progestin, which includes of COC component. Should be noted as more effective progesterones are norgestimat, levonorgestimat, desogestrel and gestogen, which presents gestalgenic component of II–III generation. Synthetic porgestines of III generation are desogestrel and gestoden have less residual and androgenic activity in accordance with progestines I and II generation. Besides that having a high bio-access in less androgenic activity, desogesterel and gestogen could be observed as progestines by chose in COC gestogen prescription to patients with EHP. By treatment purpose of EHP is used monophase preparation in low dosage.

Main evaluation of clinical effect of hormonal therapy of two groups were created prevention criteria of the main symptoms of the diseases. Nearly all patients didn't had pain in bimanual gynecological research, dyspareunia.

There were carried out COC therapy to 30 (100%) women, in our research during 6 months in nonstop regimen. As a prophylactic of endometrial hyperplasia of all patients with positive effect of provided hormonal therapy (endometrial atrophy) was prescript combined monophase oral contraceptive Midiane in low dose for prolonged regime (during 6 month of nonstop regimen from the day of SDS). Patients were observed during a year. there were provided monitoring of clinical and laboratorial results, were evaluated the dynamic of body weight of patients, AP, morphological control of uterus mucous membrane condition were carried after 6 month therapy with Midiane, were carried out also endometrial biopsy. Echographic control of endometrial thickness were provided after 3, 6 and 12 month. It attracts with its acyclic bloody discharge which found at the first 2 month in 3 (10%) patients. With this 2 patients denied to take this medicine.

During taking Midiane COC after 6 month has defined oligomenorrhea in 18 (64.2% )patients. Oligomenorrhea was diagnosed in 24 (85.7%) of examined patients at the end of the year.

Beside that during research it was clearly marked, that Midiane COC effects positive to PMS symptoms, which decrease life quality with EHP. The effeteness was been reached in 22 (74.7%) women with PMS in the provided therapy. Evaluation of clinical effectiveness of hormonal therapy were preventive criteria of main symptoms of the diseases. Complaints dynamic is been reflected on table 11.

**Table 11**

**The main complaints of the patients pre and during hormonal therapy process.**

| Complaints | Before therapy | After therapy in 6 month |
|---|---|---|
| **Menorrhagia** | **17(56,7%)** | **1(3,6%)** |
| **Metrorrhagia** | **13(43,3%)** | **-** |
| **Pain in the lower part of the abdomen** | **11(36,7%)** | **-** |
| **Pre and post menstrual discharge** | **8(26,7%)** | **4(13,3%)** |
| **Oligomenorrhea** | **4(13,3%)** | **18 (64,2%)** |
| **Amenorrhea** | **-** | **5(17,9%)** |
| **Vasomotor and emotional-vegetative symptoms** | **2(6,7%)** | **-** |

After 6 month from the starting therapy course in patients did not singed, remained profuse menstrual cycle in 1 (3.6%); there was less patients who complaints of pain in the lower part of the abdomen, which is connect with menstrual cycle from 11 (36.7%) to 0. A little amount of smear discharge per or post menstrual cycle after complete of therapy noted in 4 (13.3%) women, these

complaints were up 2 times less vasomotor and emotional-vegetative symptoms was not remained in any patients.

During taking Midiane COC body weight was decreased and further stabilized. Approximately in the 3rd month of taking medicine in 43% patient body weight decreased till 0.5 kg and more, after 6 month of taking medicine the decreasing of body weight (which remained during a year) was to 1-2 kg in 9 (32.1%) patients. Thus, antimineralocorticoid activity of drospirenone can let to stabilize body weight and not to increase them in patients with EHP.

Additional results of antimineraloccorticoid effect of drospirenone was stability of BP. Dynamic control for BP when taking Midiane COC medicine revealed tendension to its decrease in 9 (60%) from 15 who has stabile hypertension before starting the treatment.

In US examination, which was done to the patient pre and post- therapy, was given a special attention to medial uterus echo condition (U-echo), as most authors opinion, more reliable echographic criteria of the endometrial pathology is to extension of uterine cavity. Besides that, were evaluated the volume of ovaries dynamic and endometrial thickness (table 12). In US examination, which were done after 3 month and after finishing the therapy, were evaluated the volume of unferior and posterior size of medial uterus echo (U-echo), echogenity, sound- conductivity, internal structure and endometrial markers condition. Average of U-echo of examined patients group consisted after 3 month from the starting moment of the therapy 2.42 ± 0.77mm, for reliably differentiate the analogical results till treatment 11.71± 2.051mm.

There was no echoscopic sings of hyperplastic process of uterus mucous membrane in US examination, which is done after finishing the therapy. Patients, who took hormonal therapy, the research was carried out for 30-35 days after refusing the medicine. Average indexes of U-echo increased normal resulted was 3.11 ± 0.99 mm.

**Table 12**

**USE data of pre and post therapy**

| Results | Before treatment | After 3 month from the starting therapy | After 6 months |
|---|---|---|---|
| M-echo, mm | 18,1+0,9 | 5,2+0,3 | 3,11+0,99 |
| The volume of ovaries sm3 | 12,4±0,5 | 7,4+0,1 | 8,9+0,3 |
| Endometrial thickness, mm | 25,4+1,6 | 4,2±0,2 | 5,6+0,3 |

Comparative analysis of US parameters dynamics showed similar direction of U-echo results changes, volume of ovaries, endometrial thickness during and after treatment. After 3 month from the treatment time and after completing therapy the U-echo sizes were about the norm. Accordingly, to be taken COC medicine in nonstop regimen conducted to decreasing the ovaries volume, regress of endometrial hyperplasia.

For evaluation of therapy effect after 6 month applying Midiane COC was carried out histological research of endometrial tissue samples, gotten by endometrial biopsy. Has revealed that after 6 month taking the medicine the morphological signs of endometrial hyperplasia were absent in 27 (96.4%) patients, with that in 1 (3.6%) women were founded the focus of endometrial hyperplasia.

Considering remained complains to menoarrhargia, in 1 (3.6%) patients with EHP at the age of 47, treatment was prized as effective. After 6 month from the starting moment of treatment she was carried out repeated biopsy of endometrium, which is confirmed the progressing of EHP of existing

morphological type. Considering received data, the patient was offered removing the uterus.

It should be noted, we didn't find any serious negative effects and cases intolerance of used therapy. In many patients the undergone of hormonal medicine was positive. Among negative effects of hormonal therapy noted profuse bleeding. On the shade of taking Midiane they were noted in 6 patients (21.4%). With this duration of bleeding was 4.9 ± 0.2 days. The profuse bleeding volume was few, that is why therapy was not reduced.

After 3 months after finishing the treatment menstrual function was restored in 25 patients (83.3%).

After completing the therapy with the purpose of its evaluating, has been carried out separate diagnostic scratching to 17 (60.7%) patients, in 11 (39.3%) cases were carried out uterine cavity aspiration. Endometrial curvature, which is received during scratching of uterus cavity, in 15 cases evaluated as scanty, in 2 cases as moderate.

With effectiveness evaluation of the therapy was carried out histological research of endometria. In patients' group, whom were carried out hormonal therapy, morphological picture of received material in 26 (92.8%) cases were similar with endometrial atrophy, in 2 (7.1%) endometrial shape at early stage of proliferation phase.

Clinical and morphological criteria of effectiveness of provided therapy has reflected on table 13. Clinical criteria of effectiveness therapy served to prevent hyperpolymenorrhea. In morphological research of endometria evaluated the regress level of common hyperlasia and developing secretor transformation in itself.

**Table 13**

**Clinical and morphological effectiveness of hormonal therapy in 3 month after treatment.**

| | |
|---|---|
| **Full therapeutic clinical effect** | **23 (82,1%)** |
| **Histological occurance** | **1 (3,6%)** |

In 3 month after finishing the therapy the rate of comparative morphological (liquidation of glandular hyperplasia of endometrium) and clinical ( normalization of menstrual cycle) effects were noted in 82.1% patients.

Thus, taking COC in nonstop regimen in women with EH in menopause is effective and safety method of therapy.

## Conclusion

In gynecologic pathology structure of endometrial hyperplastic processes EHP was from 5 to 25%, was actual medical and social problem with highly development rate recidives and developing of malignisation (Шешукова Н.А.,Макаров И.О., Фомина М.Н. Гиперпластические процессы эндометрия: этиопатогенез, клиника, диагностика, лечение. // Акуш.и гин., 2011, №4, с. 16-21). Endometrial Hyperplastic processes of in perimenopause are more frequent cause of uterus bleeding ( Грищенко В.И., Качайло И.А., Мурызина И.Ю. Прогностические критерии пролиферативного потенциала эндометрия в перименопаузальном периоде. // Акуш. и гинек., 2009, №6, с. 33- 38). By the research results, among the patients of perimenopause age with anomalies uterine bleeding EHP has found in 54-62% women (Кузнецова И.В. Гиперпластические процессы эндометрия. – М., 2009. – с.48).

**The Goal** of the research was perfection of treatment methods of endometrial hyperplastic processes in premenopause with clinical and morphological data.

In the line of aimed tasks for 2013-2016 period were provided complex clinical and laboratorial examination and treatment of 30 patients with endometrial hyperplastic processes in premenopause period.

After receiving the results of pathomorphological research of patient with endometrial hyperplastic processes was applied hormonal therapy (Midiane COC with nonstop regimen). Control group consist of 30 women of premenopausal age, whom was planning to apply replacing hormonal therapy. These patients were carried out endometrial biopsy for preventing its pathology.

Average age of the main group patients was 45.5 ± 1.99 years, the control group was 46.8 ± 1.75 years, that shows the comparison of examined women's group by age.

Has provided gynecological diseases analysis, reproductive function of examined women with endometrial hyperplastic processes showed, that in patients with endometrial hyperplastic processes of hystermyoma were noted in considerable percent of cases in 22 (73.3%) women of the main group, in patients of the control group are 9 (30%). The average duration of diseases were similar and consist of 6.3 ± 5.3 in women with no endometrial pathology. Presence of endometriosis has founded in anamnesis 4 (13.3%) and 2(6.6%) patients of the main and control group as well. Acute and chronic endometritis (by clinical and lab-instrumental research‘s results) 4 (13.3%) patients of the main group was noted in anamnesis, and in 2(6.7%) of control group.

The therapy COC was carried in 30 (100%) women in our research during 6 months in nonstop regimen, starting from SDS day. Patients were observed during a year. proceeded monitoring of clinical- lab results: assessed the body weight dynamic, AP results, morphological control of uterus mucous membrane condition was carried out after 6 month provided endometrial biopsy. Echo graphic control of endometrial thickness was embodied after 3, 6 and 12 months. That fact is noteworthy, that acyclic bloody vessels were revealed in the first 2 months in 3 (10%) patients. With that 2 patients refused of taking medicine. After 6 month oligomemorrhea found in 18 (64.2%) patients. It was diagnosed oligomemorrhea in 24(85.7%) examined once at the end of the year.

Beside that, surely confirmed during research that Midiane COC give positive influence to PMS, which decreases life quality of patient with EHP. The effect of medicinal therapy reached in 22 (74.7%) women with PMS by the provided results. Profuse menstrual cycle remained in 1(3.6%)women and was not noted in patients ; was decreased number of patients, who has complain in the lower part of the abdomen, with menstrual cycle from 11(36.7%) till 0 after 6 months from the beginning the course. Vasomotor and emotional-vegetative symptoms didn’t retained in not a single patient.

During taking Midiane COC body mass decreased and further stabilized. Approximately on the 3 month of taking medicine in 43% patients the body mass decreased to 0.5 kg and more, after 6 month was to 1-2kg (which was kept during the year) revealed in 9 (32.1%) patients.

Dynamic control for BP while taking Midiane COC find tendention to its decreasing in 9 (60%) from having stabile increasing of BP before the treatment.

In US the average of U-echo of the examined patients group was 2.42 ± 0.77 mm after 3 month form the starting therapy, which is confirmly differ from analogical showings till the treatment 11.7 ± 2.51mm.

USE, which were carried out after the course, didn't revealed echoscopic signs of hyperplastic process of uterus mucous membrane. Average of U-echo didn't increased normal data and were 3.11± 0.99mm.

To evaluate the effect of provided therapy after 6 month of taking Midiane COC was carried out gynecological research of endometrial tissue samples, which has gotten by endometrial biopsy. It is found, that after 6 months of taking medicine morphological signs of endometrial hyperplasia were not present in 27 (96.4%) patients, with that 1 (3.6%) women found endometrial hyperplastic focuses. Considering retained complains to menorrhagia, in 1 (3.6%) patients with EHP at 47 age, the treatment was not effective. Considering of having data, patient was offered removing of the uterus.

It should be noted, we didn't find any serious negative effects and cases intolerance of used therapy. In many patients the undergone of hormonal medicine was positive. Among negative effects of hormonal therapy noted profuse bleeding in 6 patients (21.4%). With this duration of bleeding was 4.9 ± 0.2 days. The profuse bleeding volume was few, that is why therapy was not reduced.

After completing therapy in 3 month the menstrual cycle restored in 25 patients (89.3%).

After completing the course with its affectivity to 17 (60.7%) patients was carried out separate diagnostic scratching , in 11 (39.3%) cases was aspiration of the uterus.

With purpose of effectiveness evaluation of therapy carried out histological research of endometrium. In the group, which carried out hormonal therapy, morphological therapy of gotten material in 26 (92.8%) cases were similar with endometrial atrophy, in 2 (7.1%) endometrial picture in proliferation phase in early stage.

After completing therapy in 3 months the rate of both morphological ( preventing glandular endometrial hyperplasia) and clinical(normalization of menstrual cycle) effects was noted in 82.1% patients.

Thus, taking COC in nonstop regimen in women with EH at premenopause is effective and safety therapeutic method.

## The results of the conclusion.

1. Major clinical appearance EH in premenopause of women are: menorrhagia (56.7%), Metrorrhagia (43.3%), pain in the lower part of the abdomen (36.7%), pre and post menstrual discharge (26.7%) vasomotor and emotional vegetative symptoms (6.7%)
2. During histological research of curvature from uterine cavity of the patient with EH found endometrial hyperplasia in all cases with no atypia: 16 (53.3%) patients have common typical endometrial hyperplasia, 14 (46.7%) patients have severe typical endometrial hyperplasia.
3. In premenopausal age women the EH in 46.6% takes place on the back hyperesterogenia in increased correlation LH/FSH 3 times and practically unchanged content of prolactine, progesterone.
4. Patient with EH taking Midiane COC medicine in prolonged regimen (63 twice) is an effective method for therapeutical effect echievment in (82.1%) and warning clinical reoccurrence. Morphological reoccurance took place in 3.6% cases.

## Practical recommendations

1. In the presence of endometrial hyperplasia tumor in women while premenopause is shown mono phase therapy of low dosage COC in prolonged regimen. Before prescription of hormonal therapy it is necessary to do SDS with morphological meter research.
2. The scheme of nonstop COC prescription: 63 days twice.
3. Clinic and laboratory evaluation of therapy effectiveness to provide purposely in 3 months from starting therapy (complain evaluation, USE). In cases of positive dynamic absence the clinical symptomatic and presence of echoscopic signs of endometrial pathology, it is necessary to provide pathomorphological research of uterine mucous membrane, after that depending on received results, to look through the other treatment variants.
4. Effectiveness criteria of therapeutic influence is the absence of morphological signs of hyperplastic processes by histological data of endometrial research.

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