Chapter 10

Causes of Visiting Teenagers in the Pediatric and Adolescence Examining Room

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Additional information is available at the end of the chapter

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Abstract

Adolescence is the transitional period between childhood and adulthood. Depending on female gonads' function and on hypothalamic-pituitary-ovarian axis activation, results in teenager's body growth, in secondary sex characteristics' development and finally in their reproductive potential. In adolescence, the negative feedback of gonadal steroids on gonadotropins is disturbed. Teenagers presenting with dysfunctional bleedings are usually suspected of hemorrhagic ovarian cysts or endometriosis and require gynecologic examination, evaluation, and hormone therapy. It is of great importance both for teenagers and their parents to understand that hormone therapy is the first line treatment for bleeding disorders in these ages. A detailed medical history is necessary to determine the appropriate treatment plan. Primary care includes the detection of adolescents with acute or chronic pelvic pain that may be associated with endometriosis or other pathologies like mullerian duct abnormalities, imperforate hymen, ovarian teratomas, ovarian torsion, and vaginal absence or atresia. Mullerian duct abnormalities are associated with increased rates of unexplained infertility, spontaneous abortions, and pathological conditions of pregnancy. Specialists, should help teenagers in getting familiar to their bodies, to their sexuality, inform them about the sexually transmitted diseases, and safety options including vaccination and guide them in contraception issues.

Keywords: adolescence, reasons for examination, menstrual disorders, contraception

1. Introduction

Adolescence is a period of rapid physical development triggering the simultaneous secretion of various growth hormones, sexual and thyroid hormones [1]. This period occurs in people aged between 10 and 19 years, in about 18% of the world's population and this period between childhood and adolescence, which causes physiological, psychological changes, and various other health problems and problems of menstruation, is of major importance [2]. During childhood and adolescence, it is necessary for the doctor to have appropriate behavior towards the young girl and the parents when taking history and during gynecological examination. In general, it has been found that all mothers co work to obtain information, but there is some mistrust and skepticism about gynecological examination. This mistrust largely subsides after discussions, in an appropriately configured practice environment, but in a small percentage it remains accompanied by fear and, even less, it turns into neglect in the gynecological examination. The usual reasons why young girls visit the teenage gynecology clinic are as following: amenorrhea, dysfunctional bleeding, lower abdominal pain, to avoid pregnancy due to the presence and association to great problems, great early development of genital organs, breasts, hirsutism, genital anatomy outgrowth, excretion from breast nipple, symptoms from the urethra or bowel, irritation and redness in the vulva, and pain or palpable lymph nodes in the vulva [3, 4].

2. Amenorrhea

The main process that marks the start of adolescence is the onset of pulsatile excretion of GNRH. Breast growth (thelarche) is the first natural characteristic of puberty and occurs normally in the 11th year whereas the menstrual is expected to be shown 1 year later. A range of variations in the normal sequence of events among the different populations is observed. In general, significant role plays the body weight and the nutritional balance [5, 6]. Typically, menstruation begins after 2–3 years of thelarche at Tanner IV breast stage and rarely at Tanner III stage. Approximately, 96–97% of adolescent women will have menstruation at the age of 15 [6]. During the first year after menstruation, 50% of the cycles are anovulatory, also during the next 2 years, the intervals between the menstrual cycles show wide variations ranging between 21 and 45 days. The classic definition of amenorrhea includes the absence of menstruation after the 15th year. It is distinguished in primary with or without breast growth and secondary. Amenorrhea in adolescence is a reasonable concern regarding the thorough investigation in order to find the diagnosis and future fertility prognosis. Before the beginning of any hormonal therapy, it is necessary to exclude a certain number of pathological conditions in order to avoid a delayed diagnosis of all causes that in the mature reproductive age will be characterized as infertility [5]. In the case of primary amenorrhea without the development of secondary sex characteristics, the diagnosis can be made earlier, by the completion of the 13th year and is indicative of hypogonadism [5, 7]. The occurrence of primary amenorrhea is a disruption of the interaction of a large complex of processes that contribute to the appearance and normal continuance of menstruation such as normal chromosomal composition, the presence of a functioning hypothalamic-pituitary-ovarian axis, the normal endometrial

response, the anatomical integrity of the entire path of the output of the menstrual content, and sufficient supportive function of other endocrine glands such as thyroid gland and adrenal glands. In the primary amenorrhea of adolescents, there is an increased probability that the underlying pathology is the result of congenital malformations of the genital organs (60%) or endocrine disorders (40%). The most common causes of primary amenorrhea are normal delay, important weight loss, intense exercise, and virginity hymen atresia.

2.1. Clinical indications for investigation of amenorrhea in adolescence

Absence of menstruation at 15 years (complete development of the secondary sex characteristics) is an indication of amenorrhea investigation Absence of menstruation at 13 years with simultaneous absence of secondary sex characteristics (non-start breast growth) (delayed puberty) should also be investigated [8–10]. Lastly, absence of menstruation at 14 years with simultaneous coexistence of clinical disorders, such as nutritional disorders and clinical signs of hyperandrogenism needs further investigation.

Secondary amenorrhea is characterized by the absence of menstruation for 6 months in teens who previously had an unstable menstrual cycle for three or more consecutive cycles, in adolescents with a previous cycle of 21–45 days, and generally the interruption of menstruation since it had previously begun [8–11]. The most frequent cause of secondary amenorrhea is the polycystic ovary syndrome (PCOS). The most common symptoms are infertility because of anovulation and hyperprolactinemia. Regardless of the type of amenorrhea, the presence of hypertrichosis and galactorrhea, the possibility of pregnancy, the pelvic pain as well as the history of sexual contacts should be thoroughly investigated. Other parameters to be investigated also include height, body mass index, nutritional balance and estradiol, prolactin, testosterone, AMH and FSH levels. The above investigation is considered really useful for the diagnosis of underlying pathology and the distinction between hypogonadotropic hypogonadism (HH) and amenorrhea due to primary ovarian failure. At this point, hormone control plays an important role. Low levels of FSH, LH, and E2 are indicative of hypothalamic damage. High level of FSH and LH and low levels E2 are indicative of ovarian damage. High level of prolactin is indicative of prolactinoma [10–12].

The hypogonadotropic hypogonadism (HH) (hypothalamic amenorrhea) is accompanied by low levels of FSH and E2 and can be hereditary or acquired, organic or functional. In primary amenorrhea, the origin is usually genetic or even organic and the corresponding hypothalamic functional etiology is very rare [13–15]. In the last case, absence or delayed development of secondary sex characteristics is very helpful for the distinction. In the case of hypogonadotropic hypogonadism, it is necessary to perform pituitary imaging to exclude or diagnose neoplastic pathology.

If the imaging test is negative, then hypogonadotropic hypogonadism may be congenital, functional, attributed to absorption disorders, or ultimately due to chronic underlying pathology (renal or hepatic failure) [13–15]. The congenital hypogonadotropic hypogonadism is statistically very rare. It may be appeared as independent pathological entity or associated with pituitary insufficiency, either primary or as a demonstration of a syndrome. Independent HH occurs in 90% of cases with primary amenorrhea and is accompanied by absence or delayed

development of secondary sex features [13–15]. The careful investigation of clinical signs and symptoms such as anosmia or hypoxia when combined with congenital disorders in the palate or teeth is considered necessary because they may be manifestations of Kallman'syndrome. In the case of hypoxia absence, some mutations that adversely affect the functioning of the hypothalamus may be responsible [14–16]. Moreover, some congenital HHs may be associated with other disorders of pituitary function and morphological abnormalities such as the presence of ectopic pituitary tissue. Genetic mutations and polymorphisms are also involved in these cases.

In obese adolescents with amenorrhea, some rare genetic variations regarding the leptin gene or its receptor have been described. Finally, congenital HHs may be a part of various syndromes such as Prader Willi and Bardet-Biedl.

The functional hypothalamic amenorrhea is usually secondary. The abnormal background is often associated with nutritional disorders mainly related to lipid metabolism. This particular pathological condition can be a part of a chronic pathological process or a severe emotional episode that blocks the pulsatile secretion of GNRH. The first priority in case of primary amenorrhea with normal development of secondary sex features is the exclusion of pelvic pain. That is the reason why it is widely recommended application of pelvic ultrasound as well as hormone control (testosterone, estradiol, and FSH) [13–15].

When pain is observed, the possible causes may be vaginal aplasia, presence of a transverse diaphragm covering the vagina, and more often the virginity hymen atresia. In these cases, clinical examination of the abdominal wall reveals the existence of a painful mass that may be caused by the distension of the endometrial cavity (hematometra). Presence of blood in the vagina may also be seen. Ultrasound and MRI examinations always confirm the primary diagnosis [13–15].

When there is no pain, the possible diagnosis is uterine aplasia accompanied in many cases by vaginal aplasia as in Rokitansky syndrome. The incidence is very rare, 1/4000–1/5000 [13–15]. It is a syndrome that reflects abnormal development of Muller's ducts and sometimes abnormalities of the urinary tract, musculoskeletal as well as heart disorders are also observed. Levels of FSH, LH, estradiol, and testosterone hormones are normal. The ultrasound confirms the absence of uterus [12–14]. Karyotype is always XX. The differential diagnosis of uterine aplasia includes androgen resistance syndrome, which is caused by mutations in testosterone receptors, high plasma testosterone levels, and concomitant tubal aplasia as well as aplasia of the upper part of the vagina. Karyotype in these cases is XY.

In the case of painless amenorrhea, with existing uterus confirmed by ultrasound and normal breast growth, the most probable cause is polycystic ovary syndrome.

Finally, according to a review of the American Reproductive Society, 40% of primary amenorrhea is accompanied by the absence of secondary sex characteristics and high levels of gonadotropins, 30% are due to the absence of secondary sexual characteristics and low levels of gonadotropins and 30% are present with normal breast growth [17].

Secondary amenorrhea is characterized by the absence of menstruation for a period of at least 3 months in previously normally menstruating adolescents. In any case, the possibility of pregnancy must first be excluded.

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It is also necessary to investigate the history of secondary sex characteristics development, the nutritional balance, the psychological status, the weight ups and downs and the physical fitness, or the presence of hyperandrogenic signs and the rapid increase of weight during puberty. Special points are also hyperinsulinemia, galactorrhea-indicative sign of hyperprolactinemia, signs of hypercortisonemia, and black nozzle in the neck. Coexistence of hyperandrogenism is confirmed by elevated levels of total testosterone as well as of 17-OH-progesterone. In cases that confirmed the lack of hyperandrogenic signs, progesterone test, control of E2, prolactin, and FSH levels can be used for the determination of diagnosis. Oligomenorrhea (less than 8 cycles during a year) undoubtedly raises the interest for further investigation. The most frequent causes of secondary amenorrhea are functional hypothalamic disorders and polycystic ovarian syndrome. Finally, the diagnostic plan should always include the exclusion of less common causes that may also contribute to the demonstration of oligomenorrhea [10–15].

2.2. Therapy

Therapy should be mainly based on the underlying cause. If any barrier exists to menstrual flow, surgery is inevitable. It is also necessary to surgically remove androgen-secreting tumors that may be located either in the ovaries or in adrenal glands. Non -pharmaceutical hyperprolactinemia should be treated by dopaminergic agonists. When amenorrhea is caused by functional hypothalamic etiology, the treatment should include changes in dietary habits and possible special psychological support. All other cases, except of Rokitansky and the androgen resistance syndrome where there is no hormonal disorder, require hormonal therapy.

The main target is either to restore estrogen deficiency or to prevent endometrial hyperplasia in cases of anovulatory cycles [10–16]. Replacement treatment also aims to prevent distressing consequences such as osteoporosis and cardiovascular diseases.

When primary amenorrhea is not accompanied by development of secondary sex characteristics, treatment initially includes the administration of small doses of estrogen to induce puberty onset. It is then required to progressively increase the above doses until satisfactory breast growth is achieved. After the second year, it is recommended to add progestogen for at least 10 days/cycle.

When amenorrhea is secondary with normal development of secondary sex characteristics, progestogen is used to assess endogenous estrogen production. The positive test indicates adequate estrogen production and 10 days administration of progestogen allows the cycle's normalization. If the test is negative and there is also a need, treatment with contraception can be administrated starting with a low dose. Basic condition is the absence of any familiar history of thromboembolic events. If contraception is not desired, then replacement therapy is administered. This includes 17β-estradiol either orally, as skin patch, or as gel for 25 days/cycle and progestogen 10–12 days/cycle. In case of hyperandrogenism in PCO syndrome, the administration of acetate cyproterone at a dose of 50 mg/day is recommended for 21 days/month in combination with 17β-estradiol.

The presence of amenorrhea in adolescence should not be underestimated. It is advisable to investigate amenorrhea either after the 15th year or 3 years after breast growth has started.

The clinical examination always evaluates BMI, height, any hyperandrogenic, or galactorrhea signs. Laboratory investigations include estradiol, hCG, FSH as well as testosterone, and 17-OH progesterone levels.

Early diagnosis of genetic causes of hypogonadotropic hypogonadism occurs at <40%. The identification of new genes may improve the scientific knowledge in the function of hypothalamic-pituitary-ovarian axis during puberty.

In the case of hypogonadism, long-term hormone replacement therapy is recommended and sometimes psychological support is also required.

3. Polycystic ovary syndrome (PCOS)

The most frequent hormonal disorder in reproductive age's women with oligo or anovulation and hyperandrogenemia is associated with PCOS in the majority of cases. Many factors such as psychological, social, and economic could play role in the disorder of the syndrome. Moreover, the association of PCOS with metabolic syndrome and its effects represent a new challenge of interest of the syndromes in the general population. The major symptoms are:

a. Hyperandrogenemia or hyperandrogenism

b. Oligo or anovulation

c. Polycystic appearance of the ovaries during sonography [18, 19].

In PCOS, many symptoms included hirsutism, acne, alopecia, acanthosis nigricans, and obesity that are also linked to hyperinsulinemia [18–20]. One of seven teenagers (13%) has a major health problem because of obesity. Obesity is a major health problem affecting approximately 13% of teenagers. Normal body mass index (BMI) values range from 19 to 24.9 kg/m^2. Body mass index <19 kg/m^2 characterizes underweight individuals. Body mass index ranging from 25 to 29.9 kg/m^2 characterizes overweight people, 30–40 kg/m^2 characterizes obese people, and >40 kg/m^2 characterizes severely obese individuals. Menstrual cycle disorders are related to obesity in childhood and in young women. As the abdominal adipose tissue increases, increment of androgens aromatization is observed and subsequent endocrine abnormalities are appeared. Obesity is an independent factor aggravating PCOS endocrine abnormalities as subcutaneous abdominal tissue and liver contributes to extragonadal aromatization [21]. Obese women with PCOS have two types of insulin resistance, one related to the syndrome and the other related to obesity. The pancreas is involved in the mechanism of insulin resistance by increasing the release of insulin, which leads to stabilization of the glucose level in the early stage of the disease [21]. During pregnancy, the morbitity is increased with an increase in labor induction, urgent cesarean section, dystocia and abnormal presentation. The neonates are generally overweight and the risk for fetal death is increased. Moreover, diabetes during pregnancy is increased and needs follow-up. Recent data show an increased rate of overweight and obese women, specifically in the United States of the female population (64.1%) and obese women remain high (35.5%). In Europe, there is a diversity depending of the countries: low rate (6.2%) in Western and Northern Europe, high rate in Central, East and South Europe (36.5%). Oral contraceptives are the major treatment of PCOS decreasing all the

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clinical symptoms and the level of androgens. In obese adolescence, the oral contraceptive pills have a different pharmacokinetic profile with a decrease of the estrogens and progestogen clearance, but in contrary an increased SHBG was observed [22–26].

Contraceptive pills constitute the cornerstone of hormone therapy, as they promote reduction of hyperandrogenemia, hirsutism, and acne [27].

Therefore, there is a typical decreased effectiveness of contraceptive pills in obese adolescents, despite there are superior to the contraception with condoms.

3.1. Therapeutical strategy

Any other known disorders, that they are possible to cause hyperandrogenemia and oligo or amenorrhea have to be excluded. These are often associated with: nutrition, exercise, menstrual disorder treatment, metabolic syndrome and diabetes drug treatment and can be treated by contraceptive pills having progestagen with antiandrogenic action, as cyproterone acetate, dienogest, drospirenone [28, 29].

3.2. Functional uterine bleeding in adolescence

In adolescence, it is quite possible a disorder of negative regression of gonadotropins by gonadal steroids to be happened. The average age of menarche, based on recent data, has been reduced in developed as well as in developing countries over the last few decades and is attributed to various conditions, such as metabolic syndrome, eating disorders, gynecological cancer, and heart stroke diseases [30–33].

Dysfunctional bleeding is characterized by abnormal bleeding without functional impairment. It is caused by ovarian dysfunction in 10% of the cases in women of reproductive. The incidence is 10–17% among adolescents and is mainly dependent on the immaturity of the hypothalamic-pituitary-ovarian axis. They are not attributable to structural damage of the genital tract. In addition, they are observed during all the years of reproductive age.

It constitutes an exclusionary diagnosis at the onset of reproductive age and it is anovulatory almost in all cases (80–90%). The reason of the bleeding concludes the lack of cyclic secretion of progesterone resulting in continuous stimulation and endometrial hyperplasia of endogenous estradiol. Throughout of this progress the endometrium is overpowered, its perfusion capacities die resulting in necrosis, while in other places it continues to be repaired [34].

They are usually characterized as anovulatory cycles, even they can also be appeared in normal cycles as well as they are almost the half of the total metrorrhagia cases.

In some cases, asymptomatic structural abnormalities also coexist, such as polyps and subserous or intramural fibroids. They usually do not affect the whole of the endometrium and are often of high intensity without excluding the possibility of remaining drooping for several days. They are generally irregular with fluctuations in their intensity. It is quite often the first clinical manifestation of systemic hematological diseases especially in adolescents. The disorders are limited just to one of the three phases of the hemostatic procedure. In thrombocytopenia and von Willebrand's disease, there is insufficient platelet clot formation (1st phase of hemostasis) resulting in metrorrhagia [9]. Menorrhagia may occur in the rare case of VIII, XIII,

and fibrinogen deficiency (2nd phase of hemostasis), mutation of the M.T.H.F.R. (C677T) gene (LAME). In these cases, there is a lack of primary platelet clot and fibrin production. Finally, fibrinolysis (3rd phase of hemostasis) in endometrium can be also observed, especially in cases of unexplained or intense menorrhagia [9].

4. Anovulatory cycles

Female genital hormone equilibrium disorders observed either in cases of hyperestrogenism (estrogen escape bleeding) or in cases of sudden subestrogenism (interruption of exogenous administration – bilateral ovariectomy), or, finally, in cases of progesteronism (progesterone bleeding bleeding-progesterone withdrawal contraceptive). Diagnosis is often raised by exclusions (malignant diseases, genital tract, PCO, and hypothyroidism liver cirrhosis). The mechanisms involved in the pathophysiology of the above-mentioned bleeding cases are systemic in their nature, although it is possible to observe inadequacy of local hemostatic mechanisms resulting from the absence of cyclic production of progesterone and related endothelin-1, prostaglandins and other substances that contribute positively to local hemostasis of the endometrium [9]. Additionally, lack of ovulation causes unexpected bleeding, which adversely affects the quality of life of the patient. Functional hypothalamic or pituitary disorders that cause suppression of gonadotropin production, anovulation, and the approach to perimenopausal age cause typical changes in the genital cycle.

Progressively shorter cycles due to a gradual decrease in follicles and a corresponding fall in ovarian function lead to metrorrhagia [9].

5. Insufficient follicular maturation

Increased FSH levels are associated with abnormal menstrual in duration and time. Impact on adolescents is including 20–55% of the cycles in the first year and one-third of the cycles in the third year after menstruation which are still anovulatory. Anabolism is the most common cause of dysfunctional hemorrhages in adolescence and indeed it can even lead to hospital care [35]. This is due to functional immaturity of the hypothalamic-pituitary-ovarian axis.

Adolescents whose menstruation appears before the 12th year of age have in 50% anovulatory cycles during the first year, while those who are menopausal at the age of 12–13 years it is needed to pass a period of up to 3 years to make ovulation cycles. Hemorrhage due to hyperestrogenic cycles are usually characterized by histologically persistent productive endometrium and hyperplasia caused by progesterone prolonged and progesterone deficient estrogen mitotic activity [9]. The morphological changes in the endometrium are similar to those observed in women receiving estrogen replacement therapy. The origin of bleeding can be sought in the apoptosis of the layer accompanied by red blood cell extravasation, the formation of platelet thrombi and fibrin clots in the capillaries, and the existence of processes related to the reconstitution, including layer formation and hypertrophy of the regenerated epithelium. Morphological lesions are typically focal and located near or on the

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surface of the endometrium. In contrast, in cases of interruption of the E2/P relationship, they are diffuse. The exact mechanism of tissue apoptosis in hyperestrogenic endometrium is unclear. The abnormal development of the endometrium includes additional qualitative and quantitative changes in microvascularization such as spiral arterial compression and venous growth, which are often stretched, thus forming abnormal venous networks. Of particular interest is the fact that the process of neovascularization is inadequate in or near the hemorrhage focal area while adjacent intact endometrium does not show an increase in microvascularization. The abnormal morphology of microvascularization accompanies or is the cause of endometrial hemostasis disorders. Because of the lack of the arachidonic acid precursor, prostaglandin production is inadequate. Prostaglandins cause more dilation than contraction, and angiotensin-2 production is reduced. All of the above leads to the conclusion that bleeding, in these cases, is caused by vascular density disorders accompanied by structural abnormalities leading to rupture or degradation of the microvascular system. This process is followed by the release of lysosomal proteolytic enzymes from the epithelial and stromal cells and from endometrial migrating leukocytes and macrophages, while granulocytes and activated NK cells secrete perforins. In addition, the ability of contraction of basal and myometrial vessels is inadequate or absent. All of the above changes contribute to the inadequate structure and layout and ultimately to the degradation of the capillary network and constitute the major agents of extensive hemorrhage. Based on the above, the best therapeutic results are obtained when the bleeding hypertrophic-hyperplastic endometrium is excluded by performing suction biopsy or scraping. In these cases, an extensive stripping of the base layer is created followed by vasoconstriction of the arteries and arterioles as well as by tissue reconstruction. Functional hemorrhage due to progesteronism manifests as escape bleeding in women taking progestogens or using contraceptive tablets. The intensity, duration, and other features of these cases' bleeding depend on: type, dose and duration of progestogen administration, the estrogen-progestogen relationship, endogenous estradiol levels and the particular endometrial response to hormonal administration [7, 9]. Endometrial histology in these cases is predominantly influenced by progesterone and ranges between atrophy with or without cortical conversion of the layer and mixed appearance of productive and secretory elements. The greater the dose and the duration of administration, the more pronounced is the secretory type atrophy with a pronounced pro-stratum gland-layer relationship. In this case there is a corrugated endometrial layer especially in the initial periods of use containing migratory lymphocytes and macrophages as well as granular endometrial cells. All of the above lesions are associated with abnormalities of endometrial angiogenesis. These changes are accompanied by structural lesions and vasodilation leading to bleeding during the first months of use. The increased concentration of migratory leukocytes and other cells associated with immunity and the imbalance between metalloproteinases (proteolytic MMP enzymes that cause an intrauterine extracellular matrix) and their inhibitors against them, cause even greater vasodilation [7, 9]. In conclusion, the development of an abnormal and fragile network of microvascular surfaces in combination with the release of proteolytic enzymes and poor vasoconstriction due to reduced production of vasoconstrictors as a result of increased degradation by endopeptidase is the key factor in the manifestation of the above functional bleeding. Fortunately, the continuation of contraceptives decreases the frequency with the end result being usually observed only during the first 6–12 months of use.

6. Ovulatory cycles

They are related to disorders or inadequacy of local hemostasis mechanisms and decreased spiral arteriolar density. Endometrial histology varies from productive and secretory to menstrual, and the changes are not different from the corresponding premenstrual women with normal cycles. There is an increased blood flow to the endometrium whereas the levels of circulating ovarian steroids are normal. The endometrial prostaglandin production is increased with a priority to vasodilator PGF2a and angiopathic PGE2 types. Prolonged vasodilation leads to decreased platelet aggregation and increased overexpression of potential parathyroid-related vasodilatory protein. High proteolytic activity of lysosomal enzymes in the endometrium as well as fibrinolysis through increased local secretion of agents with heparin analog activity. The mechanism that triggers all these disorders is present unknown [9, 35].

6.1. Diagnostic approach

History, gynecological examination, laboratory test such as blood generation, coagulation factors, βhCG, ultrasound through genital organs, parthenoscopy, magnetic resonance, and laparoscopy.

6.2. Treatment

Adolescent medium degree functional disorders of uterus: Hb > 9gr cyclic providing of progesterones, contraceptive pills, and iron preparations. In cases of Hb < 9gr, intravenous hydration, blood transfusion, high dosage of contraceptive pills per os, potential intravenous providing available estrogens continuing usage of contraceptive pills, and iron preparations.

Activity of the estrogen-progesterinoides agents in haemostasis led to: increasing of TXA2, platelet agglutination, prothrombin, Factors VIII and X, reduction of fibronolysis, PGI_2 in endometrium.

7. Adolescent functional disorders of uterus

Metrorrhagia is a symptom, not a specific disease entity. The effectiveness of treatment is based on proper diagnosis. It is very important to establish the stabilization of ovulation cycles. Therapeutic intervention always takes seriously the young of the age [36, 37].

8. Dysmenorrhea

It is a Greek word that has prevailed in the international bibliography as painful menstrual bleeding 2–3 years after menstruation with onset of ovulation. Frequent disturbance of adolescence ED has primary—no organic damage to the pelvis and secondary—painful ER due to pelvic conditions such as endometriosis, pelvic inflammation, and congenital abnormalities of the genital system [38, 39].

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9. Explanatory theories

Theory of Hippocrates: Cervical lumen stenosis and the induced posture of stomach blood are responsible for the occurrence of dysmenorrhea. Myometric factor: increased myometrial activity and increased endometrial pressure. Neuromic factors: changing neuromuscular activity in the uterus after pregnancy may explain the reduction in menstruation pain after childbirth.

- Hormonal effect: women with anorexic cycles do not show painful menstruation.
- Prostaglandins: high levels of PGs are currently the most accepted causal theory

Increased levels of PGF2a and PGE2 and increased PGF2a/PGE2 ratio are observed in adolescents with PD. Also increased levels of LTC4, LTD4, and LTE4 angiotensins, stimulation of myometrial contractility, and increase in plasma hormone concentrations in women with dysmenorrhea [38, 39].

9.1. Psychological factors

Subjectivity and fluctuation of the pain, dysmenorrhoea very often presented in family history.

9.2. Clinical features of dysmenorrhea

Subabdominal pain, nausea, vomiting, diarrhea, irritability, headache, flatulence payment of forces, depression, and inability to concentrate are clinical features of dysmenorrhea.

9.3. Treatment of dysmenorrhea

PGs synthetase inhibitors, non-steroidal anti-inflammatory agents act by lowering levels of PGs by reducing levels of PGs, tolfenamic acid, naproxen, and mefenamic acid. The release of PGs into the menstruation blood is maximal in the first 48–72 hours of EGFR. Contraceptive pills reduce the amount of menstruation blood, through the controlled increase of the thickness of endometrial tissue. By inhibiting of ovulation, an endocrine environment with low levels of PGs is maintained.

Other therapeutic proposals are spasmolytics, analgesics, calcium inhibitors, progesterone, magnesium, GnRH analogues, leukotriene antagonists, cervical curettage, acupuncture, electricity stimulation, and psychotherapeutic methods [39, 40].

9.4. Pelvic pain

Primary care of the gynecologist specialized in child and adolescent gynecology is the investigation of women with chronic pelvic pain. The rate of disease varies among teenagers between rarity and 19–47% [41, 42]. Typical forms of chronic pelvic pain are relatively common and non-recognition may underestimate their incidence. Mostly have primary secondary dyspnea and dysmenorrheal. In girls, the gynecological examination is not feasible and the rectal examination provides little information. The ultrasound provides information on a

possible chocolate cyst, hematosalpinx, and free fluid in the Douglas space. In non-response to NSAID medication, MRI and laparoscopic approaches are recommended with a detection rate in the specific cases of endometriosis approaching approximately 50%. Endometriosis symptoms in this age group are not specific, not related to adults, but gives continuous pain and a normal menstrual cycle. Atypical forms of endometriosis are more common in teenagers and their non-recognition may underestimate their frequency [43–45].

Primary care is the detection of adolescents with chronic pelvic pain experienced by endometriosis or other pathology. Irritable bowel syndrome is a common bowel dysfunction without attributing to specific etiology. It is characterized by recurrent chronic abdominal and pelvic pain combined with bowel dysfunction either as diarrhea or constipation. It is found in 50–80% of women with chronic pelvic pain and diagnostic criteria are proposed for diagnosis criteria against Rome ii.

Another cause of pelvic pain is congenital abnormalities of the genital system. Clinical symptoms are amenorrhea, metrorrhagia, dysmenorrhea, endometriosis, repetitive abortions, in cases of pregnancy, abnormal position and presentation of fetus, and premature birth [43–45]. Treatment of abdominal pain is a challenge for the specialized gynecologist especially when an exact diagnosis has not been made. Particularly in these young people, there is a major harmonic relationship between a young doctor and his/her parents in order to find an organic cause of the reported symptomatology or in cases where there is no finding of a treatment analogous to the subjective cause [43, 44].

10. Contraceptive methods

The purpose of contraception is to prevent fertilization of the ovum from the sperm or to prevent implantation of the fertilized egg in the uterus. There are many methods of contraception for everyone to be educated. The ideal method of contraception attaches to the prevention of an unwanted pregnancy but also protects against sexually transmitted diseases. Of approximately, 3 million unwanted pregnancies that occur in the United States, 54% of these do not use contraception.

10.1. Contraceptive methods

Natural methods: withdrawal method (coitus interruptus) of approximately 57% is used in adolescent women with a failure rate of about 22% and lack of protection against sexually transmitted diseases.

1. Reversible (small time action) [46–49].
    - Men's condoms
    - Hormonal methods (contraceptive tablets, vaginal ring, transdermal patches)
    - Other methods (contraceptive diaphragm, cervical cap)
2. Reversible (long time action) [46–49].
    - Intrauterine device
    - Implants

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3. Irreversible
    - Tubal ligation
    - Seminal duct ligation
4. Emergency contraception
    - Levonorgestrel
    - Ulipristal acetate [46–49].

11. Contraceptive pills

It is a complex issue that causes family embarrassment to healthcare professionals in government officials in civil servants and young people themselves. There has been extensive effort to increase the use of contraceptive methods and in particular the condom to avoid pregnancies and sexual transmitted diseases.

Definitely it is necessary to set up Family Planning Centers for Teenagers, which must become a priority for each government. Basic award principle for contraceptive pills, as long as necessary, as little as possible [50]. Contraceptive capacity of contraceptive pills is estimated by the Pearl Index (Pearl Index). All formulations with combined oral hormonal contraception have Pearl index ≤1.25 women (years). There are several differences regarding the hormonal components contained in each formulation which may vary depending on the type, composition, quantity, and number of active tablets. Single-phase formulations contain active tablets with the same constant amount of estrogen and progestogen ratio. In contrast, the above ratio changed in the multiphase pills. Biphasic have two different combinations, the three phase and recently there are also four phases with successive decrease in the estrogen ratio and corresponding increase in the progestogen ratio. Contraceptive pills have not been associated with weight gain and mood changes. It is recommended to take single-phase pills in teenagers for their menstrual bleeding disorders [51–55].

Contraindications of contraceptive pills are BP ≥160/100 mmHg, liver disease, migraines with focal neurological symptoms, diabetes, nephropathy, neuropathy, retinopathy, or angiopathy complications are also included.

History of thromboembolism (particularly with third generation pills with drospirenone), thrombophilia, factor V Leiden mutation, factor II mutation (G20210A allele), antiphospholipid antibodies, protein C deficiency, protein S deficiency, antithrombin III deficiency, undiagnosed vaginal bleeding, and estrogen-dependent breast cancer compromise contraindications for contraceptive pills. Smoking is a relative contraindication for the use. According to FDA (April 2012), revision of contraceptive pills guidelines with drospirenone increases three times the risk of thrombosis compared to other progestogens. Clots are caused by contained estrogen.

11.1. Impact of thrombophilia

- Total population: 1 per 10,000 woman years per year.
- Contraceptive pills: 4 per 10,000 woman years per year.
- Pregnancy: 10–20 per 10,000 woman years per year [56].

11.2. Positive actions

Circulation disorders such as hypermenorrhea, hypomenorrhea, metrorrhagia restoring a normal menstrual cycle, and prolong the menstrual cycle. Dysmenorrhea decreases through the action of prostaglandin synthesis. They also improve the presence of premenstrual syndrome, premenstrual edema, irritability, anxiety, and depression.

Ovary cancer risk is decreased by about 20% per 5 years of use and 50% for 15 years.

There is no protective action for mucosal ovarian cancer. They decrease the risk of endometrium cancer by 50% every 4 years of use and 70% after 12 years. Cancer of cervix represents an independent factor with a relative risk probably due to co-factors (HPV, intercourse without condoms). According to the WHO, there is a slight increase in the relative risk for users of contraceptive pills over a period of >4 years. Higher relative risk is increased for users over 10 years. The above may be affected by the use of non-barrier methods by the number of sex partners by multiparity and alcohol consumption.

It is believed that hormonal contraception, especially estrogen as mitotic agents, enhances neoplastic process particularly in women with HPV infection. Estrogenic probably affects specific DNA sequences.

Additionally, there is a direct interaction between estrogen receptors and HPV E6 and E7 protein. The problem of the possible relationship between breast cancer and hormone therapy is still largely unresolved.

The results that are available now suggest that relatively short-term treatment (less than 5 years) does not increase the risk.

For a treatment with longer duration, the existing results based primarily on estrogen monotherapy do not allow clear conclusions without excluding the possibility that the frequency could increase under these conditions. It is difficult to evaluate the role of progestogen added to the above treatment. So, it is preferable to utilize steroid hormones with anti-mitotic activity. It is known that hydroxyprogesterone derivatives such as medroxyprogesterone acetate can inhibit tumor growth activities.

There are indications that use of contraceptive pills over a period of 10 years can cause a moderate increase of the relative risk (24%) to the oncogenic progression for breast cancer. With discontinuation, this risk decreases to 0% in 10 years. It is also gained ground the aspect that this risk is greater in women with a family history, with the risk of being limited to second degree relatives. It is unlikely, however, to incriminate only estrogen because of the fact that there are minimal estrogen receptors in normal breast epithelial cells.

The progesterone may promote the mitotic process and cause atypia. It is known that the mitotic action on MCF-7 cells of human breast cancer of 19 nor-progestogen (norethindrone, gestodene, and 3-ketodesogestrel) [56–60].

In conclusion, progestogen should be emphasized that any attempt to adapt to the clinical practice of the experimental anti-mitotic action of a pregestogen should be done very carefully. Only well-tested prospective clinical trials may answer the question whether the protective effect found in the laboratory has the potential clinical application.

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Contraceptive pills advantages include ovarian cysts treatment, endometriosis, dysmenorrhea, dyspareunia, metrorrhagia, acne and decreased androgen synthesis, hirsutismus, specific activity of estrogen and antiandrogens, mastodynia, symptom reduction mastopathy, reduction of benign mastopathy, and bone increase density [60, 61].

What do women think about birth control pills from our own child and adolescent gynecology center housed in the Democritus University Family Planning Laboratory. Positive effects: positive effect on sexual life, reliability, easy to use/comfort, less bleeding, regulation of menstruation, and less painful periods.

Negative effects: nausea, headaches, changes in mood, feeling of tension on the breasts, and increase of weight.

11.3. Action mechanism of contraceptive pills

- Suspension of implantation
- Ovulation inhibition
- Thickening of cervical mucus
- Sperm motility disorder [62, 63].

Oral contraceptive pills (OCPs) perform their action through a variety of mechanisms, through the inhibition of the mesocyclic peak of gonadotropin secretion resulting in the suppression of ovulation.

Contraceptive action is mainly exercised through the progesterone of OCPs, which cause ovulation suppression by multiple mechanisms:

- ↓ Luteinizing hormone (LH).
- The thickening of the cervical mucus and ↓ of the sperm penetration.
- ↓ of fertilization capacity of the semen, the disturbance of normal motility and occlusion of the fallopian tubes.
- Obstruction of implantation due to endometrial perforation [62, 63].

Estrogens exert their contraceptive action, but they are dose-dependent, by inhibiting the secretion of gonadotropins (FSH and LH), cause the uterus to change its secretory capacity of the cellular structure of the endometrium.

There are several differences regarding the hormonal components contained in each formulation which may vary depending on the type, composition, quantity, and number of active tablets. Single-phase formulations contain active tablets with the same constant amount and estrogen and progestogen ratios. In contrast to multiphase, the above ratio changes of biphasic have two different combinations, the three phase have three and recently, there are also four phases with successive reductions in the estrogen ratio and a corresponding increase in the progesterone ratio [62, 63].

With regard to the first few generations because the dosage did not decrease at the appropriate time, side effects such as unwanted bleeding or spotting often occurred. The second generation was more effective and longer half-life, but with increased androgenic action that helped to sexual desire, however, it could lead to hypertrichosis, acne, and dyslipidemia. The third generation retains the effectiveness of the progestogen while reducing its androgenic effect. Smaller androgenic effect also makes estrogen more effective. This however entails a greater risk for thromboembolic events [62, 63].

11.4. 4th generation contraceptive pills

The widespread use of a combination of estrogen and progesterone as a contraceptive or hormone replacement therapy has made it possible to complete large epidemiological studies that have made it possible to assess the benefits and risks that may have arisen.

Among the major advantages of use, are included primarily the reduced incidence of endometrium cancer, attributed mainly to the antimitotic progesterone activity, and secondly, the reduced frequency of ovaries cancer, due anti-gonadotropic action combination [62, 63].

11.5. Contraceptive vaginal ring

It releases daily and for 21 days 120 μg of etonogestrel and 15 μg of ethinylestradiol (nestorone ring study 15–20 μg EU + 150–200 μg nestorone).

It remains in place for 3 weeks and the fourth week it is removed for bleeding to escape. It is possible to be removed during sexual intercourse.

Existing progesterone: etonogestrel (3-keto desogestrel) 19-nortestosterone derivative.

Nestorone belongs to the norprogesterone family and is weakly active by oral administration. It does not bind significantly neither to the androgen receptor, nor to the estrogen receptor. It is a flexible, transparent silicone ring. It secrets daily 15 μg ethinylestradiol and 120 μg etonogestrel. Its diameter is 53 mm with cross section 4 mm. The duration of usage is 1 month, 3 weeks/1 week.

It is direct start fitting and has possibility to maintain up to 35 days. The next placement can be without delay. There is less interruption for a shorter duration of menstruation. Tampons, spermicide nonoxynol-9, or intravaginal miconazole should not to be used at the same time. It can be removed in less than 3 hours. It does not affect in sexual contact.

It causes breast tenderness, headaches and nausea, spotting, vaginal intolerance or hypersecretion, and unconceivable loss or misuse. There are no studies evaluating its effect on adolescent bones. There is no evidence of VTE in relation to low-dose OCPs. Ease of use has not demonstrated increased compliance or prolonged use (<30% in 6 months) [64, 65].

11.6. Evra patch contraceptives

They release EE 600 μg with norelgestromin 6 mg. They remain placed for 7 days for 3 consecutive weeks followed by 1 week without patch. It is a useful alternative method for women who hardly remember daily taking the pill because if they forget there is a 2 day error margin. It should be avoided when weight greater than 90 kg. The increased exposure to estrogen compared to oral contraceptive pills creates 1.6 and 1.2–2.2 higher probability of deep thrombosis [65, 66].

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11.7. Implants

They modify cervical mucus (viscosity in reduced amount) prevent sperm penetration and suppress endometrial growth which becomes inappropriate for implantation.

It is an ideal contraceptive method for teenagers who do not want to deal with contraception often [65].

11.8. Injectable contraceptive preparations

Injectable contraceptive preparations medroxyprogesterone acetate depot, intramuscular protection 3 months with efficacy 99.7%.

Monthly combined contraceptives estradiol cypionate and medroxy progesterone acetate depot, valerian estradiol, and norethrone acetate.

They improve dysmenorrhea increase the risk of thromboembolic events and may cause menstrual disorders [65].

11.9. Transdermal contraceptive patches evra

Transdermal contraceptive patches evra release ethinyl estradiol 600 μg with norelgestromin 6 mg. They remain placed for 7 days for 3 consecutive weeks followed by 1 week without patch it is a useful alternative for women who hardly remember daily taking the tablet because if they forget there is a 2 day error margin. They should be avoided when weight of the woman is greater than 90 kg. There is an increased exposure to estrogen compared to oral contraceptive pills 1.6 and 1.2–2.2 with higher probability of deep vein thrombosis [65, 66].

11.10. Subdermal implants

They modify cervical mucus (viscosity in a reduced amount), prevent sperm penetration, and suppress endometrial growth which becomes inappropriate for implantation. It is an ideal contraceptive method for teenagers who do not want to deal with contraception often [65].

11.11. Injectable progestogens

Injectable progestogens contain depot medroxyprogesterone acetate, intramuscular site of injection and they offer protection for 3 months with efficacy 99.7%.

Combined oral contraceptive pills estradiol cypionate and depot medroxyprogesterone acetate, valerian estradiol, and norethrone acetate.

They improve dysmenorrhea, increase the risk of thromboembolic events, and may cause menstrual disorders [67].

11.11.1. Barrier methods

- Male condoms.
- Female condoms.

- Sponge.
- Diaphragm.
- Birth control rings.
- Spermicides.

From contraceptive barrier methods, the most widespread, economic, easy to use, well accepted by both partners, with the greatest contraceptive success and the greatest protection against sexually transmitted diseases is the male condom, 75% of adolescents report using a condom with a failure rate of 18% [68].

11.12. Intrauterine contraception

Copper intrauterine device is the most effective reversible method of contraception in terms of cost-effectiveness which is the first method of contraception with a coil used in the world.

Mirena, which was released in 1997, is a type of intrauterine device with levonorgestrel that contains 52 mg levonorgestrel and yields 20 μg/24 h for 5 years.

They can cause amenorrhea or oligomenorrhea.

11.13. Innovations

Forming new IUD with less levonorgestrel that will be easily applied to nulliparous women (Femilis and Femilis slim) are under construction and they are another IUD without side arms, for easy adjustment to various sizes of uterus IUD (SPRM) (ulipristol).

Aims of intrauterine devices:

- Contraception.
- Menorrhagia.
- Endometrial protection.

11.14. Side effects

The use of IUD can cause temporarily edema, headache, tenderness, depression and breast tenderness, acne or other skin lesions. There are may also be appeared: abdominal pain in the lower part of the abdomen, vaginal discharge, nausea, functional ovarian cysts and rarely spotting, especially in the first months [69].

11.15. Mirena

Mirena is an intrauterine device effective in relation to the main indication of its usage which is contraception. It could be also used as a reliable therapeutic method of menorrhagia. In many cases, reduce dysmenorrhea. It reduces the risk of pelvic inflammatory disease and ectopic pregnancies.

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Finally, it protects woman in perimenopausal and postmenopausal periods who are under hormonal replacement therapy with estrogens from endometrial hyperplasia indicated in puerperium.

Contraindications conclude pelvic inflammatory disease. HIV and immunosuppressant are not contraindications. Risk of expulsion in women of reproductive age is 3–5% and in adolescents 5–22%.

12. Conclusion

From the above mentioned, we conclude that with the preventative gynecological control in females of young age, a prompt diagnosis and appropriate treatment, in particular congenital abnormalities of the genitals and investigation of clinical symptoms of these individuals, can be made.

Early diagnosis and treatment of ovarian tumors despite their small incidence of genital cancers up to 18 years of age is of major clinical importance because they are not always accompanied by a characteristic clinical picture.

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