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Reviews

Case Discussions

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Dear Colleagues

Reproductive health problems and concerns are often seen among female adolescents. This special issue entitled "Management of Common Gynecologic Problems of Adolescents" aims to deliver the most current and relevant information available on a variety of issues that are frequently encountered in daily practice or where difficulties may occur in the management of these problems. In addition, it is intended to provide useful information about appropriate counselling of adolescent girls when these issues present in the clinic. A team of international and national experts in this field was assembled for addressing common gynecologic concerns and how to approach management in a number of situations among adolescents.

The collaboration between pediatric endocrinologists and pediatric and adolescent gynecologists is a recurring theme in these articles and emphasizes a multidisciplinary approach to effectively manage the problems encountered during this phase of adolescence with a holistic approach.

We hope this special issue will be useful for the readers of the Journal of Clinical Research in Pediatric Endocrinology (JCRPE) and increase the opportunity for pediatric endocrinologists and gynecologists to work in collaboration and provide better health care for girls in this age group.

With Best Regards.

Guest Editors

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REVIEW

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Approach to Abnormal Uterine Bleeding in Adolescents

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İstanbul University, İstanbul Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkey

Abstract

This article reviews the current understanding and management of abnormal uterine bleeding (AUB) in adolescents. It is hoped that this review will provide readers with an approach to the evaluation and treatment of mild to severe uterine bleeding. AUB is a common problem which has significantly adverse effects on an affected adolescent's quality of life. The most common underlying condition in AUB in adolescence is anovulation. During the evaluation, pregnancy, trauma and sexually transmitted diseases must be ruled out, regardless of history. It should be kept in mind that AUB during this period may be the first sign of underlying bleeding disorders. Although observation is sufficient in the mild form of AUB, at the other end of the spectrum life-threatening bleeding may necessitate the use of high doses of combined oral contraceptives, intravenous estrogen and/or interventional procedures.

Keywords: Abnormal uterine bleeding, adolescents, heavy menstrual bleeding, oral contraceptive pills, coagulopathy

Introduction

Adolescents have frequent menstrual problems such as irregular menses, painful cycles and prolonged or heavy menstrual bleeding (HMB). Abnormal uterine bleeding (AUB) is defined as bleeding from uterine corpus that is abnormal in duration, volume, frequency and/or regularity. Due to immaturity of the hypothalamic-pituitary-ovarian (HPO) axis, AUB is common in adolescents (1,2). Furthermore, inherited or acquired bleeding diathesis may further intensify the existing hormonal imbalance and increase morbidity of the underlying condition. In addition to these problems, hyperprolactinemia, thyroid disorders and polycystic ovary syndrome (PCOS) are the common underlying endocrine disorders. AUB decreases quality of life, affects school attendance and limits sports and social activity participation (3). Although the management of this problem has evolved over time, the most important goal remains to alleviate the anxiety of both affected girls and their families and to identify the underlying medical conditions that may have chronic health effects for these girls. In this paper, the most common causes of AUB will be discussed and current management will be reviewed.

Normal Menstrual Cycle in Adolescents and Classification of AUB

Although the age of onset of puberty has tended to decrease over the past few decades, the age of menarche has remained constant at 12-13 years (4). At present, more than 90% of girls are menstruating before age of 14 years. Menarche is generally considered as anovulatory bleeding. The time required for HPO axis maturation following menarche, which is thought to result in ovulatory cycles and subsequent regular bleeding, varies between six months and three years. Due to ovulatory dysfunction, in the following months after menarche, irregular and unpredictable, heavy and prolonged, and, rarely, skipped menses for less than three months may occur (5). Thus perception of "normal" menstrual cycle may vary in these girls and their families. As in adults, menstrual cycles are between 21 and 34 days, last for seven days or fewer, with an average blood loss of 30-40 mL leading to 3-6 pads or tampon usage per day (6). HMB is the most common form of AUB and is defined as excessive menstrual blood loss that interferes with a woman's physical, social, emotional or material quality of life (7). Some additional signs of HMB include changing pad or tampon more often than every one to two hours, use

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of double hygiene protection, frequent soiling of clothes or bed sheets and blood clots more than one inch (2.54 cm) in diameter (8). The causes of HMB may be classified using the Polyp, Adenomyosis, Leiomyoma, Malignancy-Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic and Not yet classified (PALM-COEIN) classification which is divided into structural causes including PALM and hyperplasia and non-structural causes which include COEIN (9). The structural causes of HMB are rarely seen in the adolescent age group.

AUB might also be classified as acute or chronic. Acute AUB refers to an episode of heavy bleeding which is sufficient in quantity to require immediate intervention to prevent further blood loss. Abnormalities in quantity, regularity and/or timing in the last six months may all be defined as chronic AUB (10). Usually, chronic menstrual bleeding that exceeds 80 mL will result in anemia.

Clinical Evaluation

AUB in adolescents is a challenging and often neglected problem. Cycle to cycle variability, differences in menstrual hygiene, the wide variety of menstrual hygiene pads or tampons available, inconsistency in giving information about menstrual regularity and bleeding amounts make initial assessment of AUB even more difficult in these girls (11). Patients and their families may not know what is "normal" and patients may not inform their families about menstrual irregularities. In addition, most bleeding disorders may not be as obvious until menarche. Although during this period, AUB may occur more frequently due to anovulation, bleeding disorders may also accompany this condition.

Differential Diagnosis

In these girls, clinicians should evaluate the features of the menstrual cycle like a vital sign (12). An accurate history of patient's cycles is the main issue for diagnosis, to determine if her experiences are normal or abnormal. The onset of menarche, cycle length, variability over time and the amount of menstrual bleeding should be evaluated. After providing a suitable conversation environment, sexual activity should be questioned. Pregnancy and its related complications should also be part of the initial investigation in girls presenting with AUB. Although AUB is often caused by anovulatory cycles, severe bleeding may be the first sign of an underlying condition and this may be a diagnosis of exclusion. PCOS, another cause of anovulatory cycles, should be kept in mind as a common underlying etiology of AUB, since it can easily be missed in this age group (13). Excessive bleeding during menarche can usually indicate an underlying bleeding disorder, while regular but excessive bleeding may also be indicative of bleeding disorders. Von Willebrand disease, platelet function defects, thrombocytopenia and clotting factor deficiencies are the most common bleeding disorders in adolescent girls that present with HMB. Up to 36% of adolescents with AUB may have an underlying coagulopathy (14). Using a screening tool for underlying bleeding diathesis in adolescents with AUB can assist the physician.

Initial screening for an underlying disorder of hemostasis in patients with excessive menstrual bleeding should be structured by the medical history. A positive screening result comprises the following circumstances:

- Heavy menstrual bleeding since menarche
- One of the following conditions:
- Postpartum hemorrhage,
- Surgery-related bleeding,
- Bleeding associated with dental work.
- Two or more of the following conditions:
- Bruising, one to two times per month,
- Epistaxis, one to two times per month,
- Frequent gum bleeding,
- Family history of bleeding symptoms.

Patients with a positive screening test should be considered for further evaluation, including consultation with a hematologist and testing for von Willebrand factor and ristocetin cofactor.

In intermenstrual bleeding, cervicitis and hormonal contraception may be implicated. In adolescents who do not respond to standard medical therapy, structural causes of bleeding should be excluded. Table 1 for common causes for AUB in adolescents.

Physical Examination

When adolescents present with acute AUB, physical examination should focus on signs of acute blood loss and the etiology of bleeding. While tachycardia and orthostatic hypotension may be the only signs of severe anemia, it should be kept in mind that young patients will not present with clinical signs, despite severe anemia. While the presence of bruises and petechiae on the skin may indicate an underlying coagulation disorders, pallor may be seen due to anemia. In adolescents who are sexually active, trauma, foreign body, structural causes and pelvic inflammatory diseases can be investigated by pelvic and bimanual examination.

Laboratory Evaluation and Imaging

Initial evaluation of adolescents presenting with acute AUB should include screening for pregnancy, anemia, bleeding disorders, iron deficiency and thyroid disease (15). Complete blood count, blood type, cross match and pregnancy test should be first line tests. In addition, partial thromboplastin time, prothrombin time, activated partial thromboplastin time and fibrinogen level are the initial evaluation for disorders of hemostasis. All adolescents with abnormal initial test or positive screening results for disorders of hemostasis should be evaluated by assessment of von Willebrand-ristocetin cofactor activity, von Willebrand antigen and factor VIII for diagnosis of von Willebrand disease and other coagulopathies (16).

Since exogenous estrogen use may increase von Willebrand Factor concentrations into the normal range, it is necessary to perform the test either before starting hormone treatment or seven days after the end of treatment to prevent false negative results (17). If patient's history or physical examination findings are suggestive of PCOS, testosterone (free/total), DHEAS and prolactin should be evaluated.

Table 1. Differential diagnosis of abnormal uterine bleeding in adolescents

Endocrine	**Medications**
Anovulatory bleeding	Anticoagulants
Polycystic ovary syndrome	Depot medroxyprogesterone implants
Thyroid disorders	Intrauterine devices
Hyperprolactinemia	
Bleeding disorders	**Trauma**
Von Willebrand disease	**Foreign bodies**
Platelet dysfunction	
Thrombocytopenia	
Clotting factor deficiency	
Pregnancy	
Abortion	
Ectopic pregnancy	
First trimester bleeding	
Gestational trophoblastic disease	
Infections	
Cervicitis	
Endometritis	
Sexually transmitted disease	
Uterine pathologies	
Polyp	
Leiomyoma	
Adenomyosis	
Malignancy	

Sexually active adolescents should be screened for *Neisseria gonorhhea* and *Chylamidia trachomatis* infections with nucleic acid amplification tests.

Routine pelvic imaging is considered unnecessary since structural etiologies are rarely seen in this group. However, in the girls who do not respond to initial treatment, transabdominal ultrasonography may be more appropriate than transvaginal ultrasonography.

Management

Most adolescents need outpatient management and reassurance that their menstrual cycles would become cyclic and ovulatory over time. However, treatment is required when AUB causes anemia or impairs quality of life (18). In these girls, the first line treatment is generally medical. Surgical options should be reserved for girls who can't be managed by medical treatment. Acute AUB patients who are clinically unstable, have active bleeding or severe anemia should be hospitalized for management (19). A clinical decision should be made regarding intravenous crystalloid and blood or blood product transfusions, hormone treatment, and iron replacement, according to the severity of bleeding, clinical condition of the patient, hemodynamic stability and the underlying medical problem. If an underlying cause can be identified, appropriate specific treatment should be given.

Management of Girls with Acute Bleeding

Girls with active, profuse, heavy bleeding (>1 pad per hour), presence of vital signs in conjunction with evidence of hypovolemia, orthostatic hypotension or hemoglobin (Hb) concentration <8 gr/dL due to bleeding are accepted as having severe AUB and should be hospitalized. If patients can tolerate oral intake, and in the absence of contraindications of estrogen treatment, monophasic combined oral contraceptive pills (OCP) containing 30-50 mcg ethinyl estradiol, can be used every 6-8 hours until bleeding diminishes, then taper to two and then one pill daily (19). If bleeding does not decrease after the first two doses of OCP or patients are not able to take oral hormone treatment, intravenous 25 mg conjugated estrogen every 4-6 hours should be considered until bleeding ceases (20). Most adolescents respond quickly to hormone treatment and iron supplementation and also tolerate anemia better than adults. Therefore, blood transfusion should be avoided as far as possible until the occurrence of hemodynamic instability or the presence of symptoms of severe anemia. There is no established Hb concentration for transfusion requirement. Furthermore, if transfusion is to be performed, one unit of packed red cell should be given and the need

of further transfusion should be re-evaluated according to the subsequent status of the patient. Platelet transfusion is rarely required except in cases of severe thrombocytopenia or platelet disorder (21). In addition, when a deficiency of coagulation factors has been identified, clotting factors from plasma derived concentrate or recombinant agents might be needed (22). After cessation of bleeding, transition to maintenance treatment is required. High dose estrogen treatment can induce nausea and vomiting so anti-emetic agents should be begun in a prophylactic manner. If bleeding cannot be managed by these measures within 24-48 hours, consultation with a hematologist should be considered. During the maintenance period, continuous OCP (active pills only) which contain 30-50 mcg ethinyl estradiol with norgestrel or levonorgestrel (LNG), should be continued until Hb concentrations increase, or for longer in the presence of underlying bleeding disorders. In girls with a contraindication to estrogen-containing regimens, progesterone in the form of oral medroxyprogesterone acetate at a dose of 10-20 mg every 6-12 hours or oral norethindrone acetate at a dose of 5-10 mg every six hours are effective. Again, tapering of dose is begun after bleeding diminishes. Once the patient's bleeding ceases and Hb level is stabilized, the patient could be discharged from hospital after toleration for oral therapy is established. During the maintenance period, oral iron supplementation, along with dietary counseling to increase iron intake, should be given until iron stores are restored as indicated by a normal ferritin concentration. An oral dose of iron of 60-120 mg per day is recommended. Recently, evidence has been presented which suggested that daily single dose use is better than multiple daily doses (23). If there are concerns about oral iron intake, intravenous iron treatment may be initiated for these girls during the hospitalization period. In girls who have menstrual bleeding under control, iron support is usually sufficient for 3-6 months. Complete blood count and iron studies should be performed to determine when to terminate the supplementation.

Although it is known that nonsteroidal anti-inflammatory drugs (NSAIDs) decrease menstrual bleeding in premenopausal women, NSAIDs should not be prescribed to these girls because this therapy may exacerbate AUB due to underlying bleeding disorders. Tranexamic acid is an anti-fibrinolytic agent that has been shown to be as effective in decreasing menstrual blood loss as OCP and improved the quality of life in adolescents (24). Concomitant use of tranexamic acid and OCP is contraindicated according to drug information because there is a hypothetical increased risk of thrombosis. However, the increased risk of thrombosis with combined use has not been demonstrated by long-term clinical experiences (25). Thus, despite this risk, OCP and tranexamic acid combination has been used in patients who fail to respond to treatment with OCP alone. The recommended dose of tranexamic acid is 1300 mg orally or 10 mg/kg intravenously (maximum 600 mg/dose) three times daily for up to five days (26). Aminocaproic acid, another anti-fibrinolytic agent, is both less effective and has more side effects (27). Desmopressin is a synthetic analogue of the vasopressin. It increases concentrations of von Willebrand Factor and Factor VIII. It also causes platelet adhesion. It is commonly used in type 1 von Willebrand disease, hemophilia and platelet function defects in the form of a nasal spray (28).

First-line medical management may fail to result in cessation of bleeding in some patients who may require interventional procedures and further evaluation. Even in cases of life-threatening bleeding, procedures such as uterine artery embolization, endometrial ablation and hysterectomy should not be performed, as these treatment modalities may cause future infertility. In these patients, pelvic ultrasonography and pelvic examination under general anesthesia might provide further evidence for clinical decision making. If the presence of clot or decidual cast is demonstrated by ultrasonography, uterine evacuation or suction curettage might be appropriate. An alternative intervention to stop bleeding may be intrauterine balloon insertion. Studies of balloon insertion, especially in women with postpartum bleeding, have reported efficacy in controlling bleeding. A Foley catheter is a low-risk, low-cost, and readily accessible intrauterine balloon to consider for young girls and adolescents (29). Since the uterine volume of these girls is small, the amount of inflation needed for effective tamponing is judged by the amount of wall resistance felt. The balloon may remain *in situ* for 12-24 hours while other treatments are given. After the bleeding stops, the balloon of the Foley catheter is gradually and carefully emptied and completely withdrawn. There is a risk of uterine perforation, endometrial damage and infection risk with this method (30). Prophylactic antibiotics should be given, as long as the balloon remains, for prevention of infection.

Management of Girls with Mild or Moderate Bleeding

Girls with light or mild bleeding, indicated by normal Hb concentrations, should be reassured that observation is sufficient, unless there is an impairment of quality of life. NSAIDs can be used to reduce the amount of bleeding. If bleeding persists or becomes more severe, re-evaluation of the patient is required. If the Hb concentrations of these girls are found to be in the 10-12 gr/dL range, observation or

OCP are valuable therapeutic options and 60 mg daily iron treatment should be commenced. If hormonal therapy is chosen, monophasic OCP, with 30-50 mcg ethinyl estradiol content, can be used every 8-12 hours until bleeding slows, then the therapy should be tapered to one pill daily over the course of a few days and therapy should be continued for at lesat 21 days.

In the presence of moderate bleeding or Hb concentration in the range 8-10 gr/dL, oral contraceptive treatment should be initiated as described above and continued until the Hb concentration is above 12 gr/dL with at least six months of iron supplementation. In the presence of a contraindication to estrogen therapy or alternative treatment in adolescents with anemia, progesterone therapy can be an option. Available progesterone therapies are oral medroxyprogesterone acetate (10 mg/day), micronized oral progesterone (200 mg/day) or norethindrone acetate (2.5-5 mg/day), which should be given for 12 days in every cycle (31).

Long-term Management of Girls with Bleeding Disorders

After acute menstrual bleeding ceases, these girls require treatment for long-term bleeding control. In addition to diet optimization and iron supplementation, hormonal treatments are used. Hormonal treatments include OCP, oral, injectable and implantable progesterone and the LNG-releasing intrauterine device (LNG-IUD). For OCP, continuous or extended-cycle regimes are recommended for stabilization of the endometrium. Combinations of 30-50 mcg of ethinyl estradiol and levonorgestrel or norgestrel are more effective in reducing bleeding than in low-dose and new generation progesterone-containing preparations. Depot medroxyprogesterone acetate is also used for long-term bleeding control. Since there is a risk of hematoma with intramuscular administration, subcutaneous injection is recommended. To reduce the likelihood of initial breakthrough bleeding, therapy is applied more frequently than the usual 12-week cycle (32). Since daily, monthly and quarterly use of some formulas can be difficult for adolescents the LNG-IUD may be preferred. The LNG-IUD is active for up to five years after being placed in the uterine cavity. Additional benefits of the LNG-IUD are highly effective contraception, higher continuation rates and higher satisfaction rates when used for bleeding control compared with OCP in an adolescent population (33). In adolescents with bleeding disorders, the LNG-IUD has been demonstrated to be effective in controlling menstrual bleeding (34,35). Since breakthrough bleeding caused by etonorgestrel implants is a common side effect, it is not usually used for the treatment of AUB.

Conclusion

AUB in adolescents may be acceptable at the beginning of the reproductive age when menstrual cycle regularity is not established, or may be the first sign of a severe underlying bleeding disorder. Girls with AUB should be evaluated with care and a wide differential diagnosis should be borne in mind. Medical therapy is usually an effective and sufficient treatment. Generally, adolescents respond well to therapy. Hematology consultation, imaging methods and clinical intervention should be considered in patients who do not respond to treatment.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Cenk Yaşa, Funda Güngör Uğurlucan, Concept: Cenk Yaşa, Funda Güngör Uğurlucan, Design: Cenk Yaşa, Funda Güngör Uğurlucan, Data Collection or Processing: Cenk Yaşa, Funda Güngör Uğurlucan, Analysis or Interpretation: Funda Güngör Uğurlucan, Literature Search: Cenk Yaşa, Writing: Cenk Yaşa.

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REVIEW

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Dysmenorrhea, Endometriosis and Chronic Pelvic Pain in Adolescents

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Abstract

Most adolescents will experience discomfort during menstruation. Due to normalization of dysmenorrhea, there is delay to diagnosis and treatment. Non-steroidal anti-inflammatories are a first line treatment. Adolescents can safely be offered menstrual suppression with combined hormonal contraception, and progestin-only options. When the above are ineffective, gonadotropin releasing hormone agonists with add back treatment can be considered. Transabdominal ultrasound is indicated when first line treatments do not improve symptoms. Endometriosis should be considered in adolescents who experience ongoing pain despite medical treatment. If laparoscopy is performed and endometriosis visualized, it should be treated with either excision or ablation. Women with endometriosis should be counselled on menstrual suppression until fertility is desired. Management of chronic pain requires the involvement of a multi-disciplinary team.

Keywords: Dysmenorrhea, pelvic pain, endometriosis

Introduction

The majority (70-93%) of adolescents have discomfort associated with menstruation (1,2). Dysmenorrhea is the most common reason for missed school and activities (3). Up to 20-40% report missed school due to dysmenorrhea, and 40% report a negative effect on school performance and concentration (4). Adolescents with severe dysmenorrhea have impaired quality of life and are at increased risk for depression and anxiety (5). They present later for assessment, see multiple physicians, and suffer more, compared to adults (4). Functional impairment is the primary reason for seeking medical care in adolescents with dysmenorrhea (6). Health care practitioners (HCP) should not normalize dysmenorrhea. Adolescent women should be offered treatment and further investigation for ongoing pain (7).

Primary dysmenorrhea is menstrual pain in the absence of pelvic pathology.

Secondary dysmenorrhea is menstrual pain in the presence of pelvic pathology or due to a recognized medical condition.

Differential Diagnosis

Differential diagnosis for pelvic pain is seen in Table 1.

History

Information about age of menarche, cycle regularity, duration of menses, amount of bleeding, and time elapsed between onset of menarche and dysmenorrhea should be elicited. Pain history should encompass onset, duration, severity, aggravating and alleviating factors, and relationship to menses. Urinary, gastrointestinal, musculoskeletal and psychological symptoms should be documented. The degree of functional impairment, including absence/avoidance of school, social and sports activities should be explored (13). Adolescents should be interviewed with caregivers and independently; parental modeling may influence pain reporting and perception (14). Sexual history, if appropriate, should include presence of dyspareunia, history of sexually transmitted or pelvic infections, and sexual violence. Previous treatment, including medications, dosage and timing should be documented. One study reported that although 70% of adolescents took over-the-

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counter medications, only 31% followed recommended dosing, and only 16% took analgesics prophylactically (2).

Physical Examination

Height, weight, and vital signs should be recorded. Further examination can be delayed until a later visit. Prior to initiating hormonal treatment, only blood pressure must be documented (15). HCP should explain the steps and elicit frequent feedback.

Abdomen: Light and deep palpation is performed for masses and tenderness. A cotton swab can be used to assess for allodynia (16). Myofascial pain is assessed by asking the patient to contract their abdominal wall muscles while palpating an area of tenderness (Carnett's test). Increased pain indicates a myofascial trigger point as the intraperitoneal organs are protected (10).

Pelvis: The adolescent should be offered a mirror to assist with the educational gynecologic exam. Begin with examination of the external genitalia. Gentle traction of the labia can allow visualization of the introitus. A cotton swab can be used to gently apply pressure to the vaginal introitus to map out points of increased pain, indicating provoked vestibulodynia (17). Internal pelvic examination should be limited to sexually active patients, and may not be feasible due to anxiety, patient expectations, or pain (10). In adolescents that can tolerate a single digit vaginal exam, the bladder neck, levator ani, cervix, adnexa and uterosacral ligaments should be palpated for tenderness. Uterosacral nodules indicative of deep invasive endometriosis are rare adolescents (6,18). If there is concern about obstruction, a moistened cotton swab can be gently inserted into the vagina (19). Digital rectal examination may also be helpful to appreciate hematocolpos; a bulge may be palpated in the vagina.

Primary Dysmenorrhea

Primary Dysmenorrhea is associated with anovulatory cycles and usually presents 6-12 months post-menarche (8). Pain is due to increased uterine contractility and elevated prostaglandin levels as the ischemic endometrial lining is sloughed off (1,9,20).

Prevalence: Dysmenorrhea is estimated to affect 70-93% of young women (1,2).

Pathogenesis: Menstrual pain results from vasoconstriction and inflammation. Prostaglandins, leukotrienes and vasopressin are key drivers (21). Omega-6 Fatty acids, including arachidonic acid, are released with progesterone withdrawal, increasing local prostaglandin and leukotriene production (3,21,22). Prostaglandins induce myometrial contractility, vasoconstriction and uterine ischemia (3,21,22). Additional prostaglandin effects include headaches, nausea, bloating, vomiting and diarrhea (21).

Symptoms: Discomfort may begin the day preceding and continue during the initial 24-48 hours of menses (4). Nausea, vomiting, diarrhea, headaches and muscle cramps may be present. Pain can be cyclic, acyclic, and/or accompanied by urinary or bowel symptoms (20).

Investigations: Primary dysmenorrhea does not require further investigation. Routine ultrasound is not recommended unless first-line treatments fail (11,23).

Treatment: Adolescents should be counselled about the

Table 1. Differential diagnosis for pelvic pain

Gynecologic	Bowel	Genitourinary	Musculoskeletal	Psychological
Mittelschmerz	Constipation	UTI	Hernia	Anxiety, depression
Ovarian cysts	IBS	Interstitial cystitis	Myofascial pain	Physical, emotional, sexual abuse
Pelvic inflammatory disease	IBD-Crohn disease, ulcerative colitis	Urolithiasis	Neuropathic pain	Secondary gain
Ectopic pregnancy	Acute and chronic appendicitis		Nerve entrapment, injury	Somatization
Outflow tract obstruction	Adhesions from previous surgery		Pelvic floor myalgia	Substance use
Mullerian anomaly-obstructive and non-obstructive	Abdominal migraine/ functional abdominal pain		Fibromyalgia	
Vulvodynia	Meckel's diverticulum		Abdominal wall muscle strain	
Hydrosalpinges	Food intolerance			

UTI: urinary tract infection, IBD: inflammatory bowel disease, IBS: irritable bowel syndrome, Ref. 8,9,10,11,12.

menstrual cycle and pathophysiology of dysmenorrhea. Further investigations and pelvic examination are not needed prior to hormonal treatment (11,19). Smoking cessation is recommended, as exposure to tobacco smoke worsens dysmenorrhea (11). Use of a menstrual calendar (paper, e-health app) that is inclusive of pain symptoms, associated symptoms and missed activities may be helpful.

Analgesia

Non-steroidal anti-inflammatories (NSAIDs) are the preferred first line analgesics; regular use has shown a 27-35% improvement in dysmenorrhea (19,24). No specific NSAID is superior (11,21,25). Adolescents should be counselled to start with twice the regular dose followed by regular dosing (21). If menses can be predicted, NSAIDS should be started 1-2 days prior (26). It is helpful to provide written instructions; nearly 70% of adolescents consumed less than 50% of recommended daily dosing of analgesia (4). Women who experience significant neurological or gastrointestinal side effects should be offered selective COX-2 inhibitors.

Hormonal

Combined hormonal contraception (CHC) which may be oral, transdermal, or intravaginal, can be offered to adolescents who fail NSAIDs and/or require contraception (21,24). CHC may also be used as a first line option (23). CHC improve dysmenorrhea by reducing endometrial growth, menstrual fluid volume, and prostaglandin and leukotriene production through inhibition of ovulation and decidualization of the endometrial lining (3,21,27). CHC improve dysmenorrhea and reduce missed activities, and can safely be taken cyclically or continuously (10,28). Multiple studies have demonstrated improvement in dysmenorrhea with extended or continuous compared to cyclic regimens (11,15). Progestin-only options may be offered if contraindications to CHC are present. Levonorgestrel-releasing intrauterine systems (LNG-IUS) have been shown to improve both primary and secondary dysmenorrhea (11,29). LNG-IUS are safe to use in adolescent and nulliparous women (30). Please see below for further discussion of hormonal options.

Complementary

Non-medical interventions including heat, traditional Chinese medicine, acupuncture/acupressure, transcutaneous electrical nerve stimulation (TENS), yoga, and exercise should be discussed (11,19,21). Regular exercise is recommended for all patients with dysmenorrhea (11). Two randomized studies have demonstrated that heat is comparable to ibuprophen (11). Ginger, taken during the first 3-4 days of menses, was superior to placebo and comparable to NSAIDs (11). A recent review demonstrated limited effectiveness for fenugreek, fish oil, fish oil and vitamin B1, ginger, valerian, vitamin B1, sataria, and zinc sulfate (31). Small studies indicate benefit to Omega-3 fatty acid supplementation, high-dose vitamin D supplementation, and low-fat vegetarian diet (21,32). Further research is needed to support acupuncture, acupressure, and TENS (11,33). Patients using complementary medicine should be encouraged to share this with the HCP to reduce medication interactions.

Secondary Dysmenorrhea

Secondary dysmenorrhea typically appears 12 months post menarche and is associated with progressively worsening pain, chronic pelvic pain (CPP), midcycle or acyclic pain, and irregular or heavy menstrual bleeding (3,8,21). Common etiologies include: endometriosis, adenomyosis and obstructive anomalies.

Endometriosis

Endometriosis is the presence of endometrial glands and stroma outside of the uterine cavity. Prevalence in adolescents is unknown but has been estimated at 6-10% in reproductive-aged women (34). Endometrial deposits are often seen in the pelvis, but may be present in distant locations such as the upper abdomen (35). In adolescents, peritoneal and ovarian surface endometriosis is most common (36). HCP should have a high suspicion for endometriosis in adolescents with ongoing pain. Younger age has been associated with delay in diagnosis, however more recent studies suggest this is no longer the case (6,35). Approximately two-thirds of women with endometriosis experience symptoms before the age of 20 (37). Even when treated, adolescents with endometriosis experience reduced social and physical functioning compared to their peers (38). The impact on physical and mental health is greater than for young patients with other chronic illnesses (38). Estimated yearly costs for adult endometriosis in Europe, US and Canada ranges between 4000 and 12,000 USD (39).

Incidence: Endometriosis is the most common cause of secondary dysmenorrhea. It has been identified in 62-75% of adolescents undergoing laparoscopy for CPP and/or dysmenorrhea and in 70% of adolescents with pelvic pain that did not improve with NSAIDs and/or combined oral contraceptive (COC) (1,40).

Genetics: There is a polygenic multifactorial inheritance pattern to endometriosis (24). Twin studies have

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demonstrated heritability of 51-75% (1,21). Young women with a first-degree affected relative have a 7-10 fold increased risk (35). Epigenetic changes may also play a role (24).

Risk factors: These include menarche <14 yrs, shorter cycles, heavy menstrual bleeding, longer duration of menses, obesity, and early onset of dysmenorrhea (8,19,35,41). Obstructive Müllerian anomalies increase risk of endometriosis due to retrograde menstruation (8,24). However, there is often complete resolution of the endometrial implants post restorative surgery (24). Parity and breastfeeding reduce risk (35).

Implant Pathogenesis

The specific etiology of endometriosis is unclear. Six theories are described:

Retrograde menstruation: Sampson's Theory of Retrograde menstruation is the most widely accepted. Menstrual fluid leaves the uterus via the fallopian tubes and carries endometrial mesenchymal stem cells, epithelial progenitor cells and stromal fibroblasts which attach to the peritoneum (42). Supportive evidence includes endometrial implants found on dependent portions of the pelvis and increased incidence in young women with obstructive Müllerian anomalies (24,39,43). However, it does not fully explain the finding that most women experience retrograde menstruation, yet only 5-10% of adult women have endometriosis (9).

Coelomic metaplasia: Peritoneal coelomic mesothelial cells undergo metaplasia and transform into endometrial cells (9,39). This may explain the presence of ovarian endometriosis (39).

Lymphatic spread: Endometrial cells travel via lymphatic channels to implant in distant sites (43).

Hematological spread: Endometrial cells travel via the vascular system to implant in distant sites (43).

Immunologic: Endometrial tissue is able to proliferate due to a decreased cellular immunity (43) and/or women with endometriosis have increased levels of cytokines and growth factors (24).

Neonatal uterine bleeding: In this recent hypothesis, neonatal vaginal bleeding is thought to increase the risk of early-onset endometriosis. While actual bleeding is observed in 5% of newborn girls, occult bleeding may occur in 25% (42). At the time of increasing estrogen production (puberty), these endometrial cell clusters are re-activated (36).

Pain Pathophysiology

Endometriosis is a hormone mediated, neuro-vascular condition (22). The presence of endometrial tissue incites an estrogen-dependent chronic inflammatory reaction (9,20,21). Pain derives from increased prostaglandins, compression and/or infiltration of adjacent nerves (3,21,22,39). Increased expression of nerve growth factor, increased density of nerve fibers, angiogenesis and changes to innervation of the uterus may also contribute (22,35).

Clinical Presentation

Adolescents may not present with "classical" symptoms: dysmenorrhea, dyspareunia, dyschezia, endometriomas, and/or infertility. Common symptoms in young women with endometriosis include general pelvic pain, low energy and abdominal discomfort (37). Heavy menstrual bleeding, headaches, dizziness, low back pain are also more prevalent (37). Abdominal symptoms can include bloating, constipation, diarrhea, nausea, pain with defecation and pain that improves after bowel movements (6). Severe dysmenorrhea associated with missed activities should raise the suspicion of endometriosis. Onset of menstrual bleeding is not necessary for diagnosis of endometriosis; case reports have described the presence of endometriosis in premenarchal girls with pelvic pain (20).

Symptoms in adolescents with endometriosis are seen in Table 2.

Investigations

Laboratory investigations can assist with diagnosis (15,19). Initial blood work-up including complete blood count and erythrocyte sedimentation rate may indicate acute and chronic inflammation. Urinalysis and urine culture can identify urinary tract infection and renal/bladder calculus. Pregnancy test and sexually transmitted infection screen should be completed in sexually active patients. There is currently insufficient evidence to support biomarker testing (48).

Imaging

Ultrasound: Given the low probability of endometriomas in the adolescent population, there is debate on requirement for pre-operative ultrasound (7,19,43). Further, a normal ultrasound does not exclude endometriosis, as superficial endometriosis may not be visualized. Müllerian anomalies and other adnexal masses can also be visualised (12).

Transabdominal rather than transvaginal ultrasound should be ordered in non-sexually active adolescents.

Computed tomography scanning: May assist in the identification of appendicitis.

Magnetic resonance (MR): When comparing laparoscopy to MR for the detection of peritoneal endometriosis, MR lacked the likelihood ratio to be routinely used (20). Given most adolescents will be diagnosed with early disease, findings are unlikely to be apparent on MR (7). MR is not cost-effective for investigation of endometriosis.

Surgery

The gold standard for diagnosing endometriosis is tissue sample. Histological samples of suspicious lesions should be assessed, as there is a high false positive rate for visual identification only (20). Laparoscopy for diagnosis only, without a trial of medical treatments, should be avoided (20). If laparoscopy is undertaken, concurrent treatment of endometriosis should be performed (11,24). HCP may consider speculum examination, bimanual, and pelvirectal exams under anaesthesia based on patient history.

Management

Endometriosis is a chronic disease. As in primary dysmenorrhea, first-line treatment includes analgesia and hormonal therapy. Endometriosis is an estrogen-dependent disease; most therapies are aimed at supressing ovarian function (20). Most hormonal options are equivalent at reducing pelvic pain; factors such as cost and contraception should be considered in decision-making (20,22,39). CHC or progestin-only options can be offered with anticipated improvement in two thirds of women (24,39). The adolescent should keep a pain journal that logs pain, response to treatment, and other symptoms (19).

Non-steroidal anti-inflammatories: NSAIDS can be used prior to expected onset of menses. In endometriosis, there is no clear evidence of a benefit for relief of symptoms compared to placebo (49).

CHC: CHC are an ideal first choice due to documented safety, efficacy, low side effect profile and low cost (39). Adolescents with suspected or confirmed endometriosis should be counselled on menstrual suppression to prevent further endometrial proliferation (19,21,22,50). Endometrioma formation and recurrence are reduced through CHC-associated anovulation (50,51). No COC preparation has demonstrated superiority (50). Adolescents who experience ongoing dysmenorrhea with cyclic use can be transitioned to extended cycle. An randomized controlled trial (RCT) demonstrated reduced post-operative dysmenorrhea recurrence in cyclic versus non-cyclic users (52). Another RCT demonstrated improvement in pain scores for both cyclic and extended use, however discontinuation rates were higher in the continuous use group due to unspecified side-effects (53).

Progestins: These include oral, intramuscular and LNG-IUS. Progestins demonstrate 80-100 % improvement in

Table 2. Symptoms in adolescents with endometriosis

Goldstein et al (44)	Chatman and Ward (45)	Laufer et al (46)	Davis et al (47)	DiVasta et al (6)
Pain 100 %	Chronic pelvic pain 43 %	Cyclic and acyclic pain 65.6 %	Uterine cramping 100 %	Moderate or severe cramping 92.2 %
	Dysmenorrhea 82 %			
Cyclic pain 64 %		Cyclic pain 9.4 %	Cyclic pain 67 %	
Acyclic pain 36 %		Acyclic pain 28.1 %	Non-cyclic pain 39 %	Acyclic pain 65.8 %
Irregular menses 28 %	Abnormal bleeding 36 %	Irregular menses 9.4 %		
Dyspareunia 25 %	Dyspareunia 14 %			
Gastrointestinal dysfunction 21 %	Bowel dysfunction 29 %	Gastrointestinal pain 34.3 %	Constipation/ diarrhea 67 %	Nausea 70 % Vomiting 20 % More frequent BM 34.1 % Releif post bowel movement
Bladder dysfunction 5 %		Urinary tract symptoms 12.5 %		Dysuria 12.2 %
	Radiating pain 14 %		Referred pain (legs/back) 31 %	
Vaginal discharge 12 %				
	None 3.6 %			

symptoms due to anti-angiogenic, immunomodulatory and anti-inflammatory effects (22). Side effects include unscheduled bleeding, bloating, breast tenderness, weight gain, and mood changes (24,54). Depot medroxyprogesterone acetate (DMPA) and LNG-IUS are more effective at achieving menstrual suppression compared to oral regimens (28).

Oral progestins can be used to achieve menstrual suppression (Table 3) (28). Medication should be started at lowest dose and increased until menstrual suppression is achieved. Dosage adjustment and compliance is required (28). Progestin-related side effects may be more common in oral regimens (28,54). Norethindrone acetate (NETA) has demonstrated effectiveness for menstrual suppression in adolescents (55). In a Cochrane review, medroxyprogesterone was superior to danazol and equivalent to gonadotropin releasing agonists (GnRHa) at 12 months (54). Dieonogest has selective 19-nortestosterone and progesterone activity (9,56). In the adult population, it has been shown to be equivalent to GnRHa in reduction of dysmenorrhea, dyspareunia, physical symptoms and signs of endometriosis and improvement in daily activities (57). Adolescents requiring contraception should be prescribed oral progestins that are indicated for contraception.

Dosage regimens for progestin only options are seen in Table 3.

LNG is a 19-nortestosterone progestin with anti-estrogen effects on the endometrial lining, thereby inducing endometrial decidualization with resulting endometrial atrophy (58). Ovulation may not always be suppressed. When comparing LNG-IUS and GnRHa (leuprolide acetate), both demonstrate improvement in pain (20,58). Reduced recurrence of pain post-surgery is seen with LNG-IUS (19,58). It is safe to use in adolescent and nulliparous women with 96% success at insertion (30). Higher-dose LNG-IUS is associated with more effective menstrual suppression (28). Adolescents should be counselled on pain with insertion, and cramping/unscheduled bleeding that improves by three months (30).

DMPA can be used safely in adolescents. Users experience improvement in endometriosis and CPP symptoms (56). DMPA suppresses ovulation and leads to amenorrhea by inducing endometrial atrophy. Amenorrhea rates are 55% at one year, and 68% at two years (11). Unscheduled bleeding and weight gain are the most common reasons for discontinuation (59). Use beyond two years is associated with reversible decrease in bone mineral density (BMD) (8,59). At two years post-discontinuation, the BMD was similar to non-users. Further, there is no evidence to support increased risk of fractures and/or osteoporosis (59). Well-counselled adolescents may choose the benefit of symptom control over risk (60). Women using DMPA should be recommended calcium and vitamin D supplementation.

Table 3. Dosage regimens for progestin only options

Norethindrone acetate	5-15 mg daily
Medroxyprogesterone acetate	30-50 mg daily
Dienogest	2 mg daily
Depot medroxyprogesterone acetate	150 mg IM q 12 wk

wk: week, IM: intramuscular

Etonogestrel, an active metabolite of desogestrel, is available as a subdermal implant. Its primary mechanism is anovulation. Improved dysmenorrhea has been reported (59). It is safe for use in adolescents. However, discontinuation may occur due to increase in unscheduled bleeding (30). Counselling young women on common side effects prior to insertion may improve retention rates.

Anti-progestogens: Gestrinone, an anti-progestogen, inhibits production and use of progesterone (54). When compared to GnRHa, gestrinone was not as effective at six months, but more effective at 12 months (54). Small studies indicate improvement in pain. Side effects include unscheduled bleeding, acne, weight gain, and fluid retention (54).

GnRHa: GnRHa improve endometriosis-related pain by inducing a hypogonadic-state via suppression of the hypothalamic-pituitary-ovarian axis (61). Approximately 90% of users are amenorrheic (43). GnRHa may also improve pain by reducing inflammation, angiogenesis, and inducing apoptosis in endometrial cells (61). In adults, pain can be reduced by 80%, similar to DMPA and LNG-IUD (61). Side effects include hot flushes, vaginal dryness, sleep disturbance, headaches, mood changes and bone loss (21,61). Studies in the adult population suggest addition of letrozole or tamoxifen may reduce these symptoms. GnRHa use in adolescents should be considered second line, after inadequate response to hormonal treatment. For empiric treatment of pelvic pain, initiation of GnRHa should be delayed to 18 years (9). With surgically confirmed endometriosis, the initiation of GnRHa should be delayed until 16 yrs to ensure the majority of bone accrual has occurred (7,9). Intramuscular, intranasal and subcutaneous forms are available, with equivalent treatment outcomes (20). A “GnRHa flare” can occur due to an initial surge of LH and FSH, resulting in increased pain and unscheduled bleeding. To prevent flare, the initial dose should be timed with the late luteal phase (61). Flare symptoms can also be avoided by allowing three-weeks crossover when transitioning from CHC to GnRHa.

Spine BMD can be reduced by 5-8% after 3-6 months of GnRHa use; BMD may not return to baseline once treatment is complete (61,62,63). Based on the threshold theory, "add-back treatment" allows for low estrogen levels to protect bone and reduce vasomotor symptoms without activating endometriotic tissue (20). An RCT demonstrated stability in BMD at 12 months of add-back (64). Adolescence is a time of bone accrual and add-back treatment should be initiated simultaneously with GnRHa (20). This differs from the adult population, whereby add-back treatment is offered after six months. Add-back treatment does not reduce effectiveness (20,24,62). Options include conjugated equine estrogen 0.625 mg with NETA 5 mg, or NETA 5 mg alone (38,61). NETA is converted to ethinyl estradiol and was approved by the Food and Drug Administration for add-back treatment in adults (35,64). Both options have demonstrated improvement in adolescent quality of life, including improved pain, physical symptoms, and social functioning (38).

There is limited research on prolonged use of GnRHa in the adolescent population, and no current guidelines for BMD monitoring (57). Baseline BMD is not required unless there are additional risk factors for osteoporosis (61). Expert opinion suggests that for young women without additional risk factors, a dual-energy X-ray absorptiometry of hip and lumbar spine should be completed after nine months of treatment (7,8,61). BMD should be monitored every two years with ongoing treatment (8). Adolescents should be counselled on calcium and vitamin D supplementation.

Androgens: Androgens, such as Danazol, have been previously described to improve dysmenorrhea, but are often avoided due to androgen-related side effects including acne, hirsutism, weight gain, edema, muscle cramping, and worsening lipid profile (20,21,39). Danazol induces endometrial atrophy and has immunosuppressive effects (60). The European Society of Human Reproduction and Endocrinology (ESHRE) advises against the use of Danazol for treatment of endometriosis in adult women (20).

Anti-androgens: Cyproterone acetate (CPA) has anti-androgenic and anti-gonadotropic effects. It is available with estrogen in a CHC. CPA has been compared to COC, and both demonstrate improvement in pain at six months (50,56). As CPA can be associated with liver toxicity; liver function should be monitored (54). This may be an option for young women with contraindications to estrogen. Contraception is recommended in sexually active patients due to teratogenicity.

Aromatase inhibitors (AI): Over expression of aromatase has been identified in endometriotic implants (39). AI has been studied as part of combination treatment (with a progestin, CHC, or Danazol) to induce ovarian suppression (21,22). Side effects include vaginal dryness, hot flushes, and decreased BMD (20). Long term studies are needed. ESHRE suggests that AI should only be considered after hormonal treatment failure (20).

Surgery: Surgery should be considered after treatment failure extending to 3-6 months. For an adolescent, missing school/activities beyond this time can be particularly detrimental (43).

As the appearance of endometriotic lesions differs significantly in adolescents compared to adults, the operating gynaecologist should be familiar with diagnosis and treatment of endometriosis in this population (7,24,43). There is currently no evidence in adolescents suggesting that surgical treatment halts disease progression or prevents infertility (8). The American College of Obstetricians and Gynecologists recommends consideration of LNG-IUS placement at the time of laparoscopy for any patient with dysmenorrhea, chronic pain, or both (23).

Post-operative considerations: Patients should be counseled to continue hormonal treatment, as menstrual suppression reduces dysmenorrhea and endometrioma recurrence (7,20). There is no benefit to short post-operative courses of hormone treatment on pain, recurrence and fertility, thus ongoing medical treatment post-surgery is recommended unless fertility is imminently desired (19,24,50). An RCT in adults demonstrated a cure rate of 50% with surgery and 60% with combination of surgery and GnRH treatment, with reduced recurrence in combined treatment (65). Combination treatment demonstrated stability of endometriosis in 70% of adolescents after a mean interval of 29 months (1). A Cochrane Review demonstrated improved dysmenorrhea with post-operative medical treatment, however there was no effect on preventing pain recurrence when compared with surgery alone (66). Another review recommended post-operative long-term treatment with an emphasis on extended cycle, rather than cyclic use, of CHC to prevent recurrent retrograde menstruation and ovulation (50). Adolescents should be counselled on the possibility of recurrence as 30-50% of young women require repeat surgery within five years (19). Repeat surgery should be reserved for adolescents with pain more than two years post initial surgery despite ongoing medical treatment (7).

Complementary medicine: Women should be encouraged to disclose the use of complementary medicine to ensure there are no interactions with concurrent medications. Most of the adult studies described involve small sample sizes

(67). Studies have examined Vitamins B1, E, and D, Omega 3 fatty acids, magnesium and ginger with modest or no effect (11,67). A recent Cochrane review demonstrated limited effectiveness for fenugreek, fish oil, fish oil plus vitamin B1, ginger, valerian, Vitamin B1, sataria, and zinc sulfate (31). A small RCT demonstrated improvement in sleep quality, daily pain, dysmenorrhea, dyspareunia, dyschezia and dysuria with the use of melatonin (68). A Cochrane review demonstrated improvement in dysmenorrhea, reduction in associated symptoms and reduced use of additional medications with the use of traditional Chinese medicine compared to placebo (27). A small randomized-controlled sham study of Japanese acupuncture in adolescents demonstrated initial improvement in pelvic pain at four weeks, although this difference waned at six months (69). Some patients with chronic pain may find an anti-inflammatory diet improves their daily pain, provided adequate nutrient intake is achieved.

Support: Adolescents with endometriosis experience significant effects on school, work and relationships (20). Young women with chronic pain should be screened for mental health illness and offered support (38). Collaborative care encompassing pain management, behavior modification, menstrual suppression and emotional support should be encouraged (9,38). More research is needed on psychological treatment for adolescents with CPP.

Surveillance

Endometriosis induces a pro-inflammatory state affecting both pelvic anatomy and oocyte implantation (36,39), and infertility can be experienced in 30-50 % (19). Young women should be counselled about future reproductive function. Endometriosis worsens with ongoing menstruation, and patients should be counselled on menstrual suppression until pregnancy is desired (19,24). Fertility rates are improved in women treated with hormone treatment and/or surgery (65). Endometriosis Is not associated with overall increased cancer risk, but there is an increased association with ovarian cancer, specifically endometrioid and clear cell histology types (9,20,36). It should be emphasized to the adolescent and her caregivers that the overall incidence of ovarian cancer is low.

Genital Outflow Tract Obstruction

Recurrent cyclic abdominal pain in the absence of menses, or pain with first menses, should alert HCP to the possibility of abnormalities in the hymen or Müllerian structures (11). High suspicion is warranted in an adolescent with secondary sexual characteristics and amenorrhea two years beyond thelarche. Patients who are suspected to have an obstructive anomaly should be referred to a provider with expertise in this area, such as a pediatric gynaecologist. The patient can safely be placed on hormonal suppression until a qualified provider is available.

American Society for Reproductive Medicine Classification for Müllerian anomalies is seen in Figure 1 (70).

Chronic Pelvic Pain

CPP is defined as pain lasting beyond three to six months that interferes with daily function (71). Prevalence in adult women is estimated at 14-16 % (3). The differential diagnosis

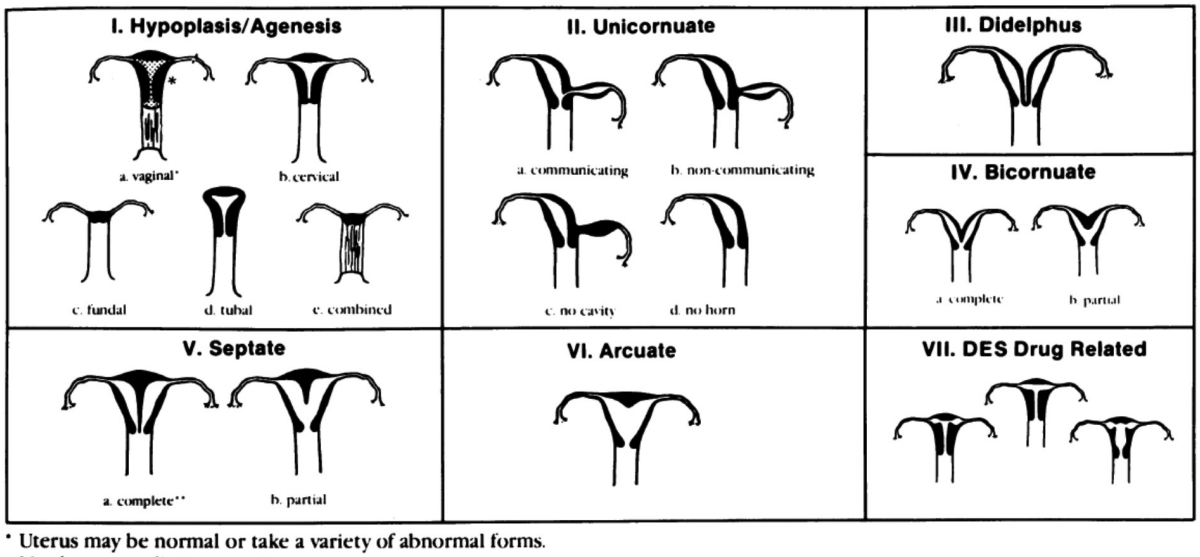

Figure 1. American Society for Reproductive Medicine Classification for Müllerian Anomalies

is similar to acute abdominal pain (Table 1). Gynecologic etiologies should be considered in post- and peri-pubertal adolescents, including endometriosis, adenomyosis, pelvic inflammatory disease, ovarian cysts, pelvic venous congestion and pelvic adhesions (3). Central sensitization, the severe experience of pain that results from multiple lower-level pain stimuli over time, can develop due to longstanding dysmenorrhea (16). Symptoms of sensitization include daily pain, nausea, dizziness, anxiety, depression, insomnia, and skin sensitivity. In CPP patients, whereby hormonal treatment or gynecological cause are absent, a musculoskeletal etiology of chronic pain was demonstrated in 67% (72). Chronic abdominal pain can precipitate hypertonicity/spasm in the abdominal wall. Attention should also be given to aggravating factors including biomechanical stressors (poor posture, footwear, heavy bags) and acute muscle strain (10). Mobilization of multi-disciplinary teams is important to address comorbidities (17). Treatment includes assessment and improvement in biomechanical stressors, heat, rest, NSAIDs, and trigger point injections (10). The adolescent may require referral to physiotherapist specially trained in pelvic floor physiotherapy.

Support

CPP can affect an adolescent at school, at home, or with peers. It is important to validate the pain and its impact. Patients should be educated on the pathophysiology of pain, and the role of pain sensitization in symptom experience (12,17). Pain catastrophizing is prominent in CPP patients and is associated with higher pain levels and impaired quality of life. Screening for mental health illness should be performed, as this can contribute to or worsen CPP. Adolescents may benefit from pharmacologic, cognitive and behavioral treatment and mindfulness training. The adolescent and involved caregivers should be involved in the generation of a treatment plan, including management of pain crisis (10,17). Treatment of mental health disorders and reduction in stress will reduce pain (12). The use of opioid narcotics should be discouraged (23). Neuropathic medications (amitriptyline, serotonin-noradrenaline re-uptake inhibitors, anticonvulsants) may be trialed (17). The adolescent should be supported in continuing with education and extra-curricular activities. Physical activity is important for overall health, and is viewed as the "best non-drug treatment for pain" (17).

Summary

The majority of adolescents will experience discomfort during menstruation. HCP should avoid normalization of dysmenorrhea, as young women are missing out on educational, social and vocational opportunities. The safety and effectiveness of NSAIDs, CHCs, progestin only options, and GnRHa have been outlined. HCP should not delay this treatment to complete physical examination and/or investigations. Patients with persistent pain despite medical treatment should be further investigated, and a diagnosis of endometriosis should be considered and a treatment plan developed. Multi-disciplinary teams should address biopsychosocial contributors to pain. CPP in the adolescent population requires further research into whether outcomes seen in the adult population can be translated and/or modified for youth. By reducing barriers to treatment and increasing the focus on high quality research in the adolescent population, we can improve the overall health outcomes for young women.

Practice Points

1. It is safe to offer menstrual suppression with combined hormonal contraception and progestin-only options to adolescents with dysmenorrhea.

2. Surgery with the aims at of diagnosis and treatment should be considered when medical treatments do not provide relief.

3. Adolescents with suspected or confirmed endometriosis should be recommended for menstrual suppression until fertility is desired.

4. In adolescents, add-back treatment should be offered concurrently with the initiation of GnRHa.

5. Young women with CPP should be followed by a multi-disciplinary team.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Nicole Todd, Design: Nicole Todd, Data Collection or Processing: Nicole Todd, Aalia Sachedina, Analysis or Interpretation: Nicole Todd, Aalia Sachedina, Literature Search: Nicole Todd, Aalia Sachedina, Writing: Nicole Todd, Aalia Sachedina.

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Where Have the Periods Gone? The Evaluation and Management of Functional Hypothalamic Amenorrhea

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Abstract

Functional hypothalamic amenorrhea (FHA) is a common cause of amenorrhea in adolescent girls. It is often seen in the setting of stress, weight loss, or excessive exercise. FHA is a diagnosis of exclusion. Patients with primary or secondary amenorrhea should be evaluated for other causes of amenorrhea before a diagnosis of FHA can be made. The evaluation typically consists of a thorough history and physical examination as well as endocrinological and radiological investigations. FHA, if prolonged, can have significant impacts on metabolic, bone, cardiovascular, mental, and reproductive health. Management often involves a multidisciplinary approach, with a focus on lifestyle modification. Depending on the severity, pharmacologic therapy may also be considered. The aim of this paper is to present a review on the pathophysiology, clinical findings, diagnosis, and management approaches of FHA in adolescent girls.
Keywords: Adolescent, diagnosis, functional, hypothalamic amenorrhea, treatment

Introduction

Functional hypothalamic amenorrhea (FHA) is defined as the absence of menses, caused by a suppression of the hypothalamic-pituitary-ovarian (HPO) axis, in which no anatomic or organic cause is found (1). It is potentially reversible, and is often seen in the setting of stress, weight loss, or excessive exercise (1,2,3). FHA can present as either primary or secondary amenorrhea. Primary amenorrhea is defined as the absence of menarche by age 15 in the presence of mature breast development, or three years after thelarche (4). Delayed puberty is defined as the absence of thelarche by the age of 13 (4). Secondary amenorrhea is defined as the absence of menses for more than three cycles in someone who was previously menstruating regularly, or longer than six months in someone with irregular cycles (5,6). FHA is the most common form of primary and secondary amenorrhea in adolescent girls (7). With specific regard to secondary amenorrhea, FHA and polycystic ovarian syndrome (PCOS) are the most common causes, other than pregnancy (1). If prolonged, FHA has potential consequences for metabolic, bone, cardiovascular, mental, and reproductive health. This article will highlight what is known about the pathophysiology of FHA, as well as the necessary steps in evaluating a patient for FHA, and the important aspects of its management.

Pathophysiology

FHA is caused by a suppression of the HPO axis. In normal puberty, gonadotropin-releasing hormone (GnRH) is released by the hypothalamus in a pulsatile fashion, and stimulates both the synthesis and secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary (7). In patients with FHA, studies have shown that GnRH secretion is suppressed, LH pulsatility is impaired (8,9,10,11), and total LH and FSH levels are reduced (11,12,13,14). FHA is therefore classified as a form of hypogonadotropic hypogonadism, which results in a hypoestrogenic state (8,12,13,14). In FHA, suppression of the HPO axis is caused by common triggers including psychological stress, disordered eating, weight loss, and excessive exercise (1,2,3).

Though amenorrhea is often associated with eating disorders such as anorexia nervosa, FHA is often found to be the underlying etiology for amenorrheic patients who

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maintain 90-110% of their ideal body weight (IBW) and who do not meet diagnostic criteria for an eating disorder (15). IBW is calculated by the Devine formula [IBW (kg) = 45.5 kg + 2.3 kg for each inch over 5 feet] (16) or can be determined by standardized height and weight tables such as the Metropolitan Life tables (17). Disordered eating is quite common in adolescent girls. In a cross-sectional study of grade 10 girls, 4.1% of girls sampled met the criteria for secondary amenorrhea and 23% disclosed disordered eating. Of the girls with amenorrhea, 40% reported fasting or purging. Interestingly, body mass index (BMI) (BMI; kg/m^2) was not significantly different between those who were eumenorrheic or amenorrheic (18). Studies have shown that patients with FHA exhibit more cognitive restraint (19), drive for thinness (12,19,20,21), and purging behaviours (21,22) compared to eumenorrheic controls.

Excessive exercise has been linked to the development of FHA (23,24). In one study, rates of secondary amenorrhea were three times higher in athletes compared to controls, with the highest rates seen in long distance runners (25). Since the early 1990s, the Female Athlete Triad (FAT) has been used to describe athletes who also present with disordered eating, osteoporosis, and amenorrhea (26). In 2017, the American College of Obstetricians and Gynecologists revised the definition of FAT to be more inclusive. The criteria are now: low energy availability with or without disordered eating, menstrual dysfunction, and low bone density (27). Though the menstrual dysfunction in FAT is thought to be hypothalamic in nature, FAT differs from FHA because athletes are not required to be amenorrheic to meet criteria for FAT. Moreover, not all patients with FHA are athletes or meet the criteria for FAT.

Onset of amenorrhea can also be seen in the setting of stress (12,28,29,30). In a study of adolescent girls with FHA, identified stressors included common life events such as changing schools, newly engaging in sexual activity, and breaking up with a boyfriend. Chronic illness of a family member and the death of a friend were also observed. Lastly, 50% of the adolescents in this study described family conflict (12). Patients with FHA have also been shown to cope less well with stress, including their autonomic responses, compared to those with PCOS and eumenorrheic controls (31).

Lastly, there may also be a genetic basis to the development of FHA. One study identified six heterozygous gene mutations in patients with FHA that are shared among patients who have congenital (idiopathic) hypogonadotropic hypogonadism, suggesting a possible vulnerability to the effects of stressors on the HPO axis. Mutations found involved the fibroblast growth factor receptor 1 gene *FGFR*, the prokineticin receptor 2 gene *PROKR2*, the GnRH receptor gene *GNRHR*, and the Kallmann syndrome 1 sequence gene *KAL1*. Such mutations were not found in healthy controls (32).

Regardless of the trigger for FHA, a common hypothesis is that an increase in corticotropin-releasing hormone (CRH), in response to stress, suppresses GnRH pulsatility (10). Patients with FHA have increased cortisol levels (10,12,13,14,20,29,33), as well as blunted responses to the injection of human CRH (hCRH) (13,29,33). In addition, the neurotransmitter γ-aminobutyric acid has also been linked to suppression of GnRH (13). Thyroid hormone changes are also noted in FHA. Patients with FHA tend to have lower total triiodothyronine (T3) and total thyroxine (T4) concentrations compared to eumenorrheic controls (11,34). However, their concentrations of free T3 and T4 may remain intact due to lower affinity of thyroid binding globulin (34). Thyroid-stimulating hormone (TSH) levels typically remain normal (11,14,34) and patients appear to be clinically euthyroid (34). Metabolic disturbances are also observed, with decreased leptin (8,12,14,19,35,36), decreased fasting insulin (12,14,35), decreased insulin-like growth factor-1 (IGF-1) (8,12), increased fasting peptide YY (19), and increased fasting ghrelin in patients with FHA (19,22). These changes reflect the overall energy deficit in patients with FHA.

Diagnosis of FHA

The diagnosis of FHA can be challenging in adolescents, as this is commonly a time when the HPO axis is developing. However, primary amenorrhea should always be investigated, as 98% of girls will achieve menarche by the age of 15 (37). Furthermore, 90% of menstrual cycles will range between 21-45 days, even in the first few post-menarchal years (38), highlighting the importance of investigating secondary amenorrhea in this age group. As FHA is a non-organic cause of amenorrhea, it is often considered a diagnosis of exclusion. Table 1 summarizes the vast differential diagnoses of amenorrhea, which should be taken into consideration.

History: A pubertal history should include onset and timing of breast and pubic hair development, as well as growth spurt. A detailed menstrual history should be obtained to characterize the type of amenorrhea and its onset. One should look for possible triggers including stressful life events, disordered eating, weight loss (regardless of initial weight), or excessive exercise. Disordered eating can include avoidance of certain foods (typically foods high in fat, sugar, and calories), restricting, and/or purging (self-induced vomiting, laxative

Table 1. Differential diagnosis of amenorrhea

Constitutional delay
Hypothalamus
Central nervous system lesion (hydrocephalus, tumor)
Chronic medical illness
Congenital hypogonadotropic hypogonadism (Kallman syndrome)
FHA (stress, weight loss, disordered eating, exercise)
Pituitary
Congenital hypogonadotropic hypogonadism
Empty Sella syndrome
Hyperprolactinemia
Iatrogenic (surgery, radiation)
Infarction (Sheehan syndrome)
Infiltrative disease
Medications (amphetamines, antidepressants, antihypertensives, antipsychotics, dopamine antagonists, contraceptives, opiates)
Neurofibromatosis
Trauma
Tumor or cyst
Thyroid
Hyperthyroidism
Hypothyroidism
Adrenal
Adrenal insufficiency
Androgen-secreting tumor
CAH
Cushing syndrome
Ovary
Androgen-secreting tumor
Gonadal agenesis or dysgenesis (ex. Turner syndrome, Swyer syndrome)
Iatrogenic (surgery, radiation)
Medications (antiandrogens, contraceptives)
PCOS
POI
Uterus
Adhesions (Asherman syndrome)
Levonorgestrel IUS
Müllerian anomaly
Pregnancy
Outflow tract
Cervical agenesis
Cervical stenosis (acquired)
Imperforate hymen
Vaginal agenesis
Vaginal septum (transverse)

CAH: congenital adrenal hyperplasia, PCOS: polycystic ovarian syndrome, POI: primary ovarian insufficiency, IUS: intrauterine system, FHA: functional hypothalamic amenorrhea, Ref. 1,3,6,41.

use, or compensatory exercising). A diet log can be helpful. If weight loss has been identified as a contributing factor, it is important to note the weight at which the patient became amenorrheic and the tempo of the weight loss. Lastly, it is important to inquire about how the weight loss was achieved, as well as how they feel about the weight loss, as this helps determine whether a formal eating disorder diagnosis should be considered. The type of exercise should be noted, as well as the duration and intensity. Patients should be asked about their past medical history, including chronic illness or malignancy. A list of medications should be obtained, and previous or current treatments with chemotherapy or radiation should be noted. A sexual history, taken alone with the adolescent in complete privacy, should be obtained, including use of contraceptives. On review of symptoms, patients should be asked about possible associated symptoms in a head to toe approach. To reiterate, one should ask about possible triggers affecting the hypothalamus, such as stress, disordered eating, weight loss, or excessive exercise. Headaches, visual disturbances, or galactorrhea could suggest the presence of a prolactinoma or another central nervous system disorder. A history of anosmia could point to Kallman syndrome. Changes in energy, temperature regulation, or bowel movement frequency could be related to an underlying thyroid disorder. Patients should be asked about signs of hyperandrogenism, such as acne or hirsutism, as this could point to a diagnosis of PCOS or late-onset congenital adrenal hyperplasia. More significant virilization (clitoromegaly, severe hirsutism, voice changes) could point to an androgen secreting tumour of either adrenal or ovarian origin. Vasomotor symptoms such as hot flashes or night sweats could be indicative of primary ovarian insufficiency (POI). Inquire about symptoms of pregnancy, such as weight gain, nausea, fatigue, vomiting, or breast tenderness. Abdominal pain, either cyclic or chronic, could indicate a possible Müllerian anomaly. Lastly, a thorough family history, including the menstrual history of the biological mother, should be obtained. Questions about possible triggers and sexual history should be reserved for the confidential portion of the interview. Commonly, the "Home environment, Education and employment, Eating, peer-related Activities, Drugs, Sexuality, Suicide/depression, and Safety from injury and violence-HEEADSSS" format is used (39).

Physical examination: The physical examination should first begin with a general inspection of the patient's well being. The patient's height and weight should be measured and plotted on growth curves that ideally have previously been completed by the referring or primary care provider in order to facilitate comparisons and trends. The BMI (kg/m^2) should be calculated and plotted. Vital signs should

include blood pressure and heart rate. Hypertension and tachycardia can be seen in hyperthyroidism or Cushing syndrome, whereas hypotension and bradycardia can be seen in hypothyroidism, adrenal insufficiency, and severe eating disorders. Look for stigmata of Turner syndrome (low hairline, webbed neck, wide carrying angle, shield chest, and nevi, including facial nevi). Look for signs of restrictive or purging behaviours, which include cachexia, erosion of dental enamel, parotid gland swelling, vellus hair, Russell's sign (calluses on the knuckles) and hypercarotenemia (yellowing of the skin). A visual field examination and fundoscopy is recommended, particularly if there are concerns regarding central nervous system symptoms in the history. Palpate the thyroid gland for a goiter or nodules and examine for other signs of thyroid disease (exophthalmos or proptosis, lid lag, hair or nail changes). Palpate the abdomen for masses. Look for signs of insulin resistance (acanthosis nigricans), hyperandrogenism (acne or hirsutism), or virilization (male pattern hair loss, change in muscle mass distribution, clitoromegaly, or voice deepening). Complete Tanner staging should be done to document pubertal development (40). The papilla and surrounding breast may also be examined for residual signs of galactorrhea. Perform an external genital examination with the aid of labial traction to assess for a patent hymen and lower vagina. This examination can also aid in determining the extent of estrogenization of the vulva. Typically, a reddened and thin hymen is seen in an estrogen-deficient state, whereas a light pink and plumper hymen is seen in the presence of adequate estrogen levels. The presence of leukorrhea can also point to adequate estrogenization. Lastly, a bimanual examination can be performed in patients who are sexually active, to palpate for a uterus and to rule out an adnexal mass. Typically, patients with FHA will have a physical examination within normal limits.

Endocrinological investigations: Initial blood work-up should include measurement of the beta subunit of human chorionic gonadotropin concentration, regardless of the disclosed sexual history, to rule out pregnancy. FSH, LH, estradiol, prolactin, and TSH concentrations should also be measured routinely. If there are signs of hyperandrogenism on examination, an androgen panel should be ordered, including total and free testosterone, androstenedione, and dehydroepiandrosterone sulfate, along with a 17-hydroxyprogesterone concentration, preferably in the early morning (1,3,41). Assessment of cortisol status may also be considered, based on presenting features. See Table 2 for a summary of laboratory findings in FHA.

A progesterone withdrawal challenge can be given to aid in the diagnosis. Five to 10 mg of medroxyprogesterone acetate are given for five to 10 days, after which the patient should experience a withdrawal bleed (41). A positive test is indicated by vaginal bleeding within two to seven days of completing the course of progestin (6). A negative test, or a lack of bleeding, may suggest an outflow tract abnormality or a hypoestrogenic state, as estrogen is responsible for thickening the endometrial lining (43). Scant withdrawal bleeding or spotting suggests marginal levels of endogenous estrogen production (6). Unfortunately, experts caution routine use of the progesterone withdrawal challenge, as it may be unreliable in determining the degree of estrogenization as this test is associated with false negative withdrawals (1,3,43,44).

Radiological investigations: An ultrasound of the pelvis is helpful to identify the presence of a uterus and ovaries, and to rule out an adnexal mass. If a Müllerian anomaly is suspected, magnetic resonance imaging (MRI) of the pelvis, or a 3D transvaginal ultrasound, if the patient is coitarchal, may better characterize the specific anomaly (45,46,47). Head imaging with computed tomography or MRI is not typically required unless the adolescent girl presents with galactorrhea (+/- hyperprolactinemia), headaches or visual disturbances, suggesting a possible intracranial lesion (1,41,48). It may also be indicated if there is a negative progesterone withdrawal challenge (4).

Due to the risk of osteopenia and osteoporosis associated with hypoestrogenism, patients with prolonged amenorrhea, of six months or more, should be considered for baseline bone mineral density (BMD) assessment measured by dual-energy X-ray absorptiometry (DEXA/DXA) scan and lateral spine radiograph to assess for asymptomatic vertebral fractures (15,41,49,50,51,52,53). In adolescents,

Table 2. Typical hormone pattern in functional hypothalamic amenorrhea

Hormone	Level
Pituitary	
FSH	Low
LH	Low
TSH	Low-Normal
PRL	Normal
Ovarian	
Estradiol	Low
Testosterone	Low-Normal
AMH	Normal

FSH: follicle stimulating hormone, LH: luteinizing hormone, TSH: thyroid-stimulating hormone, PRL: prolactin, AMH: anti-Müllerian hormone, Ref. 11,12,13,14,41,42.

BMD Z-scores are used as these values are adjusted for age and gender. They must also be further interpreted in relation to the patient's body size, ethnicity, and pubertal staging or skeletal maturity (defined by bone age) (53). There is no absolute BMD Z-score threshold that can be used alone to define osteoporosis. Rather, a diagnosis of osteoporosis requires the presence of both a clinically significant fracture history (≥3 long bone fractures at any age up to 19 years old) and a BMD Z-score <-2.0. However, a BMD Z-score >-2.0 does not to preclude the possibility of skeletal fragility, and in the setting of a low-trauma vertebral fracture, there is no BMD Z-score requirement to make a diagnosis of osteoporosis (54). Evaluation of the BMD Z-score trajectory, based on serial measurements over time, provides valuable information about which patients are at risk for fractures (declining BMD Z-scores), versus those who may be showing signs of recovery (53). BMD should be repeated every six to 12 months to assess for trajectory of BMD Z-score, in patients where risk factors remain present. Spine radiographs should also be monitored at a similar interval to assess for asymptomatic vertebral fracture (or immediately if symptomatic), particularly if there is decline in BMD Z-score (53).

Other investigations: A karyotype should be performed if a chromosomal abnormality, such as Turner syndrome is suspected and/or if gonadotropins are elevated. If gonadotropins are elevated and POI is diagnosed, other testing would be required including autoimmune antibodies and Fragile X testing.

Management

The menstrual cycle has been recognized as an important vital sign in adolescent girls (55,56), and the absence of menses may be an indication of compromised overall health. As such, the main goal of management in FHA is the resumption of menses.

Lifestyle modification: Addressing possible triggers such as weight loss, disordered eating, or excessive exercise is a primary focus in the management of FHA. In one study by Kondoh et al (29), patients with FHA related to weight loss were treated by a nutritionist for at least six months. 54.0% of these patients resumed menses with an average recovery time of 19.4±5.0 months. A small yet statistically significant increase in BMI was observed before resumption of menses in these patients. However, there has been debate over whether a critical increase in BMI is required to resume menses. A common recommendation in the literature is that a 1-2 kg weight gain from current weight, or a 5% increase in body weight, can result in the resumption of menses and improve BMD in patients with FHA. This recommendation is based on two small studies (57,58). In a study by Kopp-Woodroffe et al (57), three out of four amenorrheic participants resumed menses after a 20-week program. The program involved incorporating one rest day per week and a nutritional supplement to improve overall energy balance. In another study by Lindberg et al (58), four out of seven amenorrheic participants in a 15-month program resumed menses and had a small, statistically significant increase in BMD. Their program included a reduction in exercise duration and calcium supplementation. Larger prospective studies would be beneficial in confirming these results.

Specifically in amenorrheic female athletes, a multidisciplinary approach, which includes nutritional therapy, psychological therapy, and modification of exercise regimen has been recommended (59,60).

In all patients with FHA, if lifestyle modification is the primary treatment modality, a follow up should be done every two to three months to determine whether the desired effect is being achieved (60).

Psychological therapy: Adolescent girls and young adult women with FHA have been shown to cope less well with stress (31), and are also at a higher risk of depression (50). In the study by Kondoh et al (29), patients with FHA related to psychogenic stress, aged 15-33, were treated with psychoeducation which focused on stress management. A greater proportion of these patients recovered compared to those with weight-associated FHA; 81.8% versus 54.0%. Their average time to recovery was also slightly shorter at 17.2±4.1 months versus 19.4±5.0 months. A small randomized controlled trial (RCT) looked at the effect of a 20-week intervention with cognitive based therapy (CBT) in patients with FHA (61). In this study, the eight patients randomized to the CBT arm had a higher rate of ovarian activity (87.5%) compared to those eight patients that were in the observation arm (25.0%). Ovarian activity was determined by measuring plasma estradiol and progesterone levels, in order to confirm ovulation. BMI did not significantly change during the intervention. CBT has also been shown to have an impact on metabolic health in these patients. In a follow-up study by Michopoulos et al (62), patients randomized to the CBT arm had an improvement in cortisol, TSH, and leptin concentrations compared to those in the observation arm.

Other forms of psychological therapy have been studied. In a small prospective study, 12 patients with FHA, aged 20-33, were given a 45-70 minute hypnotherapy session and then observed for 12 weeks (63). Nine patients (75%) resumed menses, and one patient became pregnant during this time.

All patients also reported increased general well-being and improved self confidence.

Though studies looking at psychological therapy in FHA have been small, the effects of therapy are promising and are unlikely to result in harm. Therefore, psychological therapy may be considered as part of the multidisciplinary treatment of patients with FHA.

Pharmacological therapy: The main role of pharmacological therapy in FHA is to promote bone health and prevent the development of osteoporosis. A lack of estrogen during premenopausal years has been linked to decreased BMD. This is based on studies looking at the outcomes of premenopausal women undergoing bilateral oophorectomy (64,65). In one study, vertebral bone loss could be detected as early as six months post-operatively (64). An increase in the frequency of fragility fractures of the radius and femoral neck was also observed (65). Similarly, in patients with FHA, the associated hypoestrogenic state can result in reduced bone density (15,50,51). In young women less than 20 years of age, missing even 50% of menstrual cycles can result in a significant decrease in BMD (52). Therefore, studies have looked at the effects of hormone replacement therapy on BMD in patients with FHA.

A systematic review by Liu and Lebrun (66) summarized ten studies evaluating the impact of hormone therapy on BMD in women with FHA. They found seven studies which demonstrated a positive effect of combined oral contraceptives (COCs) on BMD (67,68,69,70,71,72,73), two studies that showed no effect (74,75), and one case report where a negative effect was observed (76). Of the studies that showed a positive effect, two were small RCTs (67,68). Hergenroeder et al (67) showed a significant increase in both the total BMD and lumbar spine BMD of five patients receiving 35 µg ethinyl estradiol (EE) + 0.5-1 mg norethindrone, compared to five controls. Castelo-Branco et al (68) showed a significant increase in lumbar spine BMD in 24 patients taking 30 µg EE + 0.15 mg desogestrel and 22 patients taking 20 µg EE + 0.15 mg desogestrel, compared to 18 control patients who showed a decrease in BMD. Of the studies that showed no effect, one cohort study looking at female long distance runners, found no difference in BMD after one year in nine patients who started on a COC (75). However, in the same study 11 patients with FHA who were not using a COC showed a significant reduction in BMD over the same time period. Currently, the Endocrine Society has recommended against using COCs for the sole purpose of improving BMD, due to conflicting evidence. Instead, a trial of short-term transdermal estrogen with a cyclic oral progestin is recommended in amenorrheic adolescents who have not been successful with lifestyle modification, and who are not in need of COCs for contraception (41).

To date, the majority of evidence for the positive effects of transdermal estrogen on BMD comes from research involving patients with anorexia nervosa (77,78). However, its use in patients with FHA is attracting interest and has started to be studied. Zanker et al (76) published a case report of a 24-year-old amenorrheic athlete, whom they followed for 12 years. They measured her body weight every three months and her BMD by DXA every 11-13 months. After being on COCs for five years, the BMD of her lumbar spine and proximal femur declined by 9.8% and 12.1%, respectively. Her weight dropped concomitantly from 45.1 to 41.4 kg. Over the next 3.7 years, she was treated with transdermal estrogen and an oral progestin. Her lumbar spine BMD gradually increased by 9.4%, despite a further 0.8 kg decline of body mass. In the last 2.9 years of the study, she continued the transdermal estrogen, gained a total of 8.1 kg of body mass, and had a 16.9% increase in her proximal femur BMD. Furthermore, an RCT by Ackerman et al. (79) from 2019 showed an improvement in BMD in athletes with oligo-amenorrhea receiving transdermal estrogen. In this study, 43 patients were randomized to receive a 100 mcg 17β-estradiol transdermal patch twice weekly with cyclic micronized progesterone (200 mg, 12 days per month), 40 patients to receive a daily pill with 30 µg EE + 0.15 mg desogestrel, and 38 patients received no hormonal treatment. All patients also received 800 IU of vitamin D and ≥1200 mg of calcium per day. BMD was assessed at baseline, six, and 12 months. Patients randomized to the patch arm had significantly higher spine and femoral neck BMD Z-scores at 12 months compared to the pill and the no treatment arm, and higher hip BMD Z-scores than the pill arm. The results of this landmark study are promising and lend support to the use of transdermal estrogen in patients with FHA.

In amenorrheic adolescents, 1200-1500 mg of calcium supplementation (80) as well as vitamin D 400-1000 IU (1) are recommended daily to support bone health. However, other therapies such as testosterone or bisphosphonates are not currently recommended to improve BMD in patients with FHA (41,81), as the literature available focuses mainly on patients with anorexia nervosa and the current evidence is limited.

Fertility: Patients with FHA may experience escape ovulation and therefore contraception is important if they do not desire pregnancy (41). In addition, adolescents with FHA may inquire about future fertility. Ovarian reserve is typically normal in these patients, as evidenced by their normal anti-Müllerian hormone (AMH) levels (42). In

patients who desire pregnancy, ovulation induction with pulsatile GnRH is the current gold standard (82,83,84,85). When compared to injectable gonadotropins, chances of conception are higher after six cycles of pulsatile GnRH at 96% versus 72% for injected gonadotropins based on life table analysis (82). Furthermore, injectable gonadotropins are associated with a higher rate of multiples (14.8% versus 9.3%), though the finding was not statistically significant (82). These results were more recently replicated in a study by Dumont et al (84) which showed a per patient conception rate of 65.8% with pulsatile GnRH versus 23.5% with gonadotropins. Though the trend favouring pulsatile GnRH is the same in both studies, the conception rates in the Dumont et al study are significantly lower. This may be explained by the differences in study populations between these studies, with lower BMI and baseline gonadotropin levels in the Dumont et al (84) study. The mean BMI in Dumont et al was 18.5 kg/m^2 (pulsatile GnRH group) and 18 kg/m^2 (gonadotropin group), whereas in Martin et al (82) it was 24.3 kg/m^2 (pulsatile GnRH group) and 24.5 kg/m^2 (gonadotropin group). Baseline LH, FSH, and estradiol levels were also lower in Dumont et al (84). Naltrexone, an opioid antagonist, has also been studied. GnRH secretion has been found to be suppressed by endogenous opioids (86). It was hypothesized that GnRH pulsatility could therefore be stimulated by opioid antagonism. Though naltrexone has been shown to increase GnRH pulsatility and increase rates of ovulation (86,87,88,89), its use has not become standard practice.

Cardiovascular considerations: Patients with prolonged FHA may be at higher risk of cardiovascular complications in the future (90). Studies in pre-menopausal adult women have shown hypothalamic hypoestrogenism is associated with a higher risk of coronary artery disease (91). Other possible effects include vascular endothelial dysfunction and reduced regional blood flow, as was shown in young amenorrheic athletes (92). These athletes were also found to have abnormal lipid profiles, including elevated total cholesterol and low-density lipoprotein cholesterol (92). As a follow-up study, Rickenlund et al (93) investigated the effects of using a COC (30 µg EE + 0.15 mg levonorgestrel) on these cardiovascular endpoints in amenorrheic athletes. While an improvement in vascular endothelial function after nine months of COC use was found, the lipid profile did not significantly change, with the exception of a small increase in high-density lipoprotein cholesterol. As this study was small, the authors indicated the need for larger, long-term studies to determine the clinical importance of their findings. As of now, the majority of recommendations surrounding cardiovascular health of patients with FHA focus on the lifestyle modifications that can be made to resume menses (90).

Novel therapies: Studies are now focusing on the underlying metabolic abnormalities within FHA to direct therapy. Small RCTs have looked at the effects of treatment with recombinant human leptin. Welt et al (94) demonstrated an improvement in serum estradiol, increased levels of free T4, and IGF-1 with administration of recombinant methionyl human leptin (r-metHuLeptin; starting dose 0.08 mg per kilogram of body weight per day) subcutaneously for two to three months. Three out of eight women (37.5%) resumed ovulatory cycles, which the authors stated was higher than the expected rate of spontaneous ovulation of 10%. In a small RCT, recombinant human leptin (metreleptin; starting dose 0.08 mg per kg of body weight per day) administered subcutaneously over 36 weeks, increased estradiol levels and decreased cortisol levels compared to placebo (95). Patients receiving recombinant human leptin in this study were also more likely to resume menses compared to controls (70% versus 22.2%). In both studies, markers of bone formation were also found to be increased, though BMD did not change significantly (94,95). The administration of kisspeptin has also been studied, and while acute administration appears to stimulate release of LH and FSH, chronic administration results in tachyphylaxis. Thus, the authors concluded that acute administration of kisspeptin may have therapeutic potential in patients with FHA (96). The Endocrine Society has recommended against the use of leptin or kisspeptin in the management of patients with FHA, as more research is needed in this area (41).

Conclusion

FHA is a common cause of both primary and secondary amenorrhea in adolescent girls. Common triggers include stress, weight loss, and excessive exercise. As FHA is a diagnosis of exclusion, a comprehensive workup should be performed to rule out anatomic and organic causes of amenorrhea. Prolonged FHA can have negative consequences on many aspects of a young women's health, including metabolic, bone, cardiovascular, mental, and reproductive implications. The main goal in these patients is the resumption of menses. Lifestyle modifications are the first line focus for adolescent girls with FHA and a multidisciplinary approach, including a pediatric gynecologist and/or endocrinologist, pediatric sport psychologist, and sport dietician is beneficial. Pharmacological therapy can be considered in order to promote bone health, with transdermal estrogen being a promising option for patients. Further research on novel agents, such as recombinant

human leptin and kisspeptin, is required before considering their routine use in patients with FHA.

Ethics

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Authorship Contributions

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REVIEW

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Contraception for Adolescents

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Abstract

Although pregnancy and abortion rates have declined in adolescents, unintended pregnancies remain unacceptably high in this age group. The use of highly effective methods of contraception is one of the pillars of unintended pregnancy prevention and requires a shared decision making process within a rights based framework. Adolescents are eligible to use any method of contraception and long-acting reversible contraceptives, which are "forgettable" and highly effective, may be particularly suited for many adolescents. Contraceptive methods may have additional non-contraceptive benefits that address other needs or concerns of the adolescent. Dual method use should be encouraged among adolescents for the prevention of both unintended pregnancies and sexually transmitted infections. Health care providers have an important role to play in ensuring that adolescents have access to high quality and non-judgmental reproductive health care services and contraceptive methods in adolescent-friendly settings that recognize the unique biopsychosocial needs of the adolescent.

Keywords: Adolescent, contraception, family planning, long acting reversible contraception, counselling, contraceptive services, pregnancy in adolescence/prevention and control

Introduction

Adolescents, defined by the World Health Organization (WHO) as individuals between the ages of 10-19 years (1), represent almost one-fifth of the world's population. During adolescence, young people navigate numerous physical, cognitive, emotional, and behavioural changes as they acquire increasing autonomy and experiment in many areas. Experimentation may include alcohol or drug use, smoking, and sexual activity, all of which may be associated with sexual and reproductive health risks such as unintended pregnancy and sexually transmitted infections (STIs).

The United Nations and the WHO consider that access to safe, voluntary family planning is a human right because it is essential for promoting gender equality, advancing the autonomy of women, and reducing poverty (2,3). The WHO has identified key elements in quality of care in family planning which include: having choice among a wide range of methods; patient-provider relationships based on respect for informed choice, privacy, and confidentiality as well as the cultural and religious beliefs of the young woman; providing evidence-based information on the effectiveness, risks, and benefits of the different contraceptive methods; having technically competent trained health care workers; and having convenient access to a range of relevant services (2). The WHO also states that no method of contraception is contraindicated on the basis of age alone (4). These position statements extend to adolescents who also have the right to sexual and reproductive health services, including contraceptive care and counselling. However, access to contraceptive education and information and the availability and accessibility of contraceptive methods may be affected by the complex dynamics of social, cultural, political, and religious influences, particularly for adolescents.

Sexual Behaviour and Unintended Pregnancy

In most Western countries, the median age of first intercourse is around 17 years. By age 18, 60% of females will have had sexual intercourse and by age 20 years

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almost 80%. Many have had more than one partner (5,6,7,8). Adolescents have the lowest level of contraceptive knowledge and use (9). Initiation of sexual activity while they lack adequate knowledge and skills to protect themselves places adolescents at higher risk of unwanted pregnancy, unsafe abortion, and STIs (10). Although there appears to be an increase in contraceptive use at first intercourse, many adolescents still do not use any method of contraception at first intercourse or do not continue to use contraception consistently (7,11). The most commonly used method of contraception at first intercourse is the male condom, which is important from the STI prevention perspective but is less reliable as a contraceptive method due to typical use failure rates that are significantly higher than those seen with other contraceptive methods (12).

Unintended pregnancy in adolescents can have major consequences for the young woman, her family, and society. The use of effective contraceptive methods is a cornerstone of adolescent pregnancy prevention. Although adolescent pregnancy rates are decreasing worldwide, adolescent mothers make up 11% of births (13). Although there are variations in cultural norms around age of marriage and childbearing, the majority of adolescent pregnancies are unintended (9,14,15). Adolescent pregnancy contributes to maternal and child mortality, with complications from pregnancy and childbirth being the leading cause of death for girls aged 15-19 years (13). Adolescents who give birth face significant socioeconomic challenges. Adolescents at greater risk of unintended pregnancy include those who are living in poverty, with low education and fewer employment opportunities, and marginalized populations. Pregnancy itself is an important opportunity to counsel on future contraceptive plans, as rapid repeat pregnancy is common among adolescent mothers (16). The Centers for Disease Control (CDC) Medical Eligibility Criteria for Contraceptive Use (MEC) provides guidance on post-partum contraceptive options (17).

Barriers to Contraceptive Access and Use

Barriers to accessing contraceptive information and methods include social or culture taboos, legal restrictions, health care provider (HCP) attitudes, and healthcare systems (9,10). The acceptability and availability of contraception for adolescents varies by region and even by countries in the same region. Adolescents may experience barriers accessing contraception including inconvenient medical clinic hours, financial restrictions, lack of confidentiality, and lack of provider training. HCPs themselves may act as medical barriers by imposing their own personal values/moralistic beliefs on the adolescent, by applying inappropriate medical contraindications on recommendations for contraceptive use, by delaying initiation of contraception unnecessarily (i.e. waiting until the next menses or until STI screening results are available), by requiring unnecessary investigations prior to contraceptive initiation (i.e. by erroneously insisting on a Pap smear prior to starting contraception), or by perpetuating unfounded myths about contraceptive use (18). HCPs should ensure that they have the necessary skills and knowledge to provide unbiased, non-judgemental, evidenced-based, adolescent-friendly sexual health and reproductive health care and to be able to dispel common myths and misperceptions about contraceptive use (Table 1) (9).

The cost of contraception services and methods is a potential barrier for adolescents. Contraception may be prohibitively costly for an adolescent and the need for parental financial assistance may compromise confidentiality. Although contraception is provided at no cost in some countries, in other countries contraception is covered by private healthcare and/or by the patient paying directly. Provision of contraception at no cost may remove one financial barrier but does not guarantee high rates of utilization. Nonetheless, universal subsidies for contraception appear to be cost-effective (25). The annual direct cost estimates for unintended pregnancy are $320 million in Canada and $4.6 billion in the United States (26,27). Contraceptive non-adherence accounts for 69% of this cost. Cost models have shown that provision of/switching to long-acting reversible-contraceptives (LARC) would reduce contraceptive failures and lead to cost neutrality within 12 months (26,27). The Contraceptive CHOICE Project determined that provision of free contraceptives to adolescents reduces teen pregnancy, teen birth, and abortion (28) while yielding significant cost savings (29). The CHOICE Project also found that when cost is removed, the majority of adolescents (~70%) would choose LARC.

Contraceptive Counselling

There should be no restrictions on the ability of adolescents to receive complete and confidential contraceptive services. An assurance of confidentiality will increase the willingness of adolescents to disclose sensitive health information and seek health care advice, while a loss of confidentiality can negatively impact an adolescent's participation in sexual health services (30). Confidentiality, including its scope and limits, should be discussed with adolescents and caregivers, and reiterated once the adolescent is alone. Regrettably, adolescents' legal rights to confidential family planning services vary by region and change over time (31). Adolescents should also be aware of instances where confidentiality may need to be breached (32). HCPs should

consult local laws regarding confidentiality and age of consent, which may vary by region. An adolescent's choice of contraception should be respected, and contraception should never be coercive.

The clinic should be welcoming to adolescents, ideally with flexible scheduling, convenient times (timed around school), and age appropriate visual aides (33). Scheduled follow-up visits are important to ensure method acceptability and ongoing contraceptive adherence.

HCPs should engage in a shared decision making process with adolescents. There are many suggested approaches to contraception counselling. The CDC suggest that sexual history taking should include the "5Ps": Partners, Practices, Protection from STIs, Past history of STIs, and Pregnancy Prevention (33). This can help HCPs and adolescents work toward a contraceptive plan that is focussed on anticipatory guidance, education, and disease prevention. Another approach to contraception counselling is the "GATHER" approach where the HCP **G**reets and builds rapport, **A**sks questions and listens, **T**ells her relevant information to help her make an informed choice, **H**elps make a decision and provides other related information, **E**xplains the method in detail including its effectiveness, potential side effects, and how to use it, and lastly has the patient **R**eturn for advice or further questions (34). Another approach to contraception counselling can be found in Table 2. Adolescents should be asked about intimate partner violence, and specifically about reproductive coercion.

HCPs should counsel on all available contraceptive options without bias. Effectiveness, advantages and disadvantages should be discussed. Adolescents should be advised that failure rates are highest for user dependent methods (e.g. natural family planning, withdrawal, condoms, oral contraceptives) (12). LARC methods act continuously and are less user-dependent [e.g. contraceptive implants and intrauterine contraceptives (IUCs)]. A recent Cochrane review did not find significant differences amongst hormonal contraception, levonorgestrel releasing system (LNG-IUS), and copper intrauterine device (Cu-IUD), although the studies were small, and of low to moderate quality (35). Anticipatory discussion around anticipated menstrual side effects can reduce discontinuation of the shorter acting methods (36).

The WHO has developed a tiered system to discuss contraception (Figure 1) (37):

Tier 1: LARC are methods that do not rely on the user.

Tier 2: Methods that rely on consistent use daily (pill), weekly (patch), every three weeks (vaginal ring), every three months depo-medroxyprogesterone acetate (DMPA).

Table 1. Contraceptive myths and misperceptions

Myth	Fact
The COC pill causes weight gain and acne	Placebo-controlled trials have not shown an association between COC use and weight gain. Acne improves in most women using COCs due to a decrease in circulating free androgens
A pelvic exam is required prior to initiating contraception	With the exception of an IUC (which requires a pelvic exam for insertion), pelvic examination is not required prior to starting a contraceptive method
It is important to "take a break" from the COC every few years	It is not necessary to take a "pill break". Unless medical conditions arise that contraindicate its use, the COC may be continued until pregnancy is desired or a woman wishes to switch to another contraceptive method
COCs and IUCs can affect future fertility	When COCs or IUCs are discontinued, a woman quickly returns to her baseline fertility
IUCs cannot be used in adolescents or in nulliparous women	IUCs can be safely used by adolescents and nulliparous women
IUCs increase the risk of ectopic pregnancy	IUCs work primarily by preventing fertilization so IUC users have half the risk of ectopic pregnancy compared to women not using contraception (19)
IUCs do not have any non-contraceptive benefits	The LNG-IUS is associated with a decrease in menstrual flow and less menstrual cramping. All IUCs are associated with a decreased risk of endometrial cancer (20)
COCs cause cancer	COCs are associated with a decreased risk of endometrial and ovarian cancer and potentially colorectal cancer. The risk of cervical cancer may be increased in COC users compared with non-users. Data on breast cancer risk with COC use is conflicting but many studies have failed to demonstrate an increased risk of breast cancer or breast cancer mortality in COC users (21,22,23)
IUCs can only be inserted during menses	An IUC can be inserted at any time during the menstrual cycle provided that pregnancy or the possibility of pregnancy can be ruled out (24)

COC: combined oral contraceptive, IUC: intrauterine contraceptive, LNG-IUS: levonorgestrel-releasing intrauterine system, IUCs: intrauterine contraceptives

Tier 3: Methods that rely on user during sexual activity (male and female condom, spermicide, natural family planning), or immediately after [emergency contraception (EC)].

Many international organizations have recommended moving to a tiered approach to contraceptive counselling, whereby HCPs present contraceptive options in order of contraceptive effectiveness and start the contraceptive discussion with Tier 1 LARC methods (8,33,38). Contraceptive effectiveness is one of a woman's most important considerations when choosing a contraceptive method (39) and using top tier methods would achieve the highest effective contraception. However, while effectiveness is a paramount characteristic, it is important that tiered counselling focused on "LARC-first" does not become too directive or coercive, particularly in vulnerable populations (40). In a rights-based family planning framework, the choice of contraception should be made in collaboration with each individual adolescent taking into account safety, effectiveness, accessibility, and affordability while respecting her personal beliefs, culture, preferences, and ability to be adherent (25).

Age alone is not a contraindication to any contraceptive method (2,32,41). HCPs should address common myths and misperceptions (Table 1) as well as common side effects. Adolescents may fear weight gain, bleeding, acne, and mood side effects, while their parents may fear effects on future fertility and the risk of cancer. Regardless of the method of contraception chosen, adolescents should be counselled on the importance of the use of latex condoms to reduce the risk of STI acquisition (dual method) (25,38).

Starting Contraception

Most contraceptive methods can be initiated at any time during the menstrual cycle provided that pregnancy or the possibility of pregnancy can be ruled out (Table 3) (41,42). The "Quick Start" method refers to starting a method immediately rather than waiting for the next menstrual

Table 2. Contraceptive counselling in the adolescent

Be Welcoming
- Use adolescent friendly language and material
- Acknowledge the need for confidentiality
- Remain unbiased and non-judgmental

What to Ask
- Reproductive and sexual history, including previous and current use of contraception
- Medical history including any specific medical conditions or medications that may be contraindications to contraceptive use
- Her current relationships, partners, and whether she has any concerns
- What is she currently doing to prevent pregnancy?
- How important is it to her to avoid pregnancy currently?
- Her ability and motivation to use contraception regularly and correctly
- Her needs and expectations from a contraceptive method
- The level of support she has at home or from her partner
- Whether she needs to hide her use of contraception
- Would she prefer to have periods or to not have periods?

Be Sure to Check
- Her awareness of methods and whether she already as a preference
- The accuracy of her knowledge
- Methods matching her needs and expectations have been discussed
- The identified potential options are acceptable to her
- How will she pay for contraception?
- Is STI screening appropriate?
- Does she have any fears or concerns?

What to Tell
- How the method works, how effective it is, how to use it consistently and correctly, what to do if they miss/are late for a dose, and when to seek medical attention?
- How it will affect her menstrual cycle?
- What are the non-contraceptive benefits?
- Potential side effects and what to do if they occur?
- When to return for a follow-up visit?

period. Waiting to initiate contraception may place an adolescent at an increased risk of unintended pregnancy. Starting contraception immediately/at the time of the visit, has been associated with improved short-term compliance and is not associated with an increased incidence of breakthrough bleeding or other side effects (43,44). When the possibility of pregnancy is uncertain, the benefits of starting a combined hormonal contraceptive (CHC) (CHC: COC, vaginal contraceptive ring, contraceptive patch) likely exceed any risk. Thus CHC can be started immediately and a follow-up pregnancy test arranged in 2-4 weeks.

Table 3. Criteria for being reasonably certain a woman is not pregnant

A woman has no signs or symptoms of pregnancy and meets one of the following criteria:

- Is ≤7 days after the start of a normal menses
- Has not had sexual intercourse since the first day of her last normal menses
- Has been using a reliable method of contraception consistently and correctly
- Is ≤7 days post-abortion (spontaneous or induced)
- Is < 4 weeks post-partum
- Is exclusively breastfeeding, amenorheic, and < 6 months post-partum

If any of the above criteria are met, a pregnancy test is not required. In most other cases, a negative high sensitivity urine pregnancy test will reasonably exclude pregnancy

Ref. 41.

Adolescents who choose to Quick Start contraception when a very early pregnancy cannot be completely excluded can be reassured that current evidence does not demonstrate an adverse impact of contraceptive hormone exposure on either fetal development or pregnancy outcomes (45,46). When using the Quick Start method, back-up contraception (barrier method and/or abstinence) should be used for the first seven consecutive days of contraceptive use unless it is initiated on the first day of menses (42). Adolescents may choose to start hormonal contraception on the first day of the next menstrual cycle or do a "Sunday start". Starting on the first day of the menstrual cycle allows an adolescent to be reasonably sure that they are not pregnant. Initiating on a Sunday allows for a withdrawal bleed to occur on a Monday, assuming a seven-day hormone-free interval (HFI). CHCs, injectable progestins, or contraceptive implants may be started immediately after a surgical or medical pregnancy termination (47). An IUC can be inserted immediately after first or second trimester abortion.

In asymptomatic patients, there is no requirement for a pelvic exam prior to initiating contraception. Pap smear screening recommendations have changed in recent years and vary by region, but most no longer advocate for Pap smear screening in adolescents; some bodies recommend delaying screening until age 21 in sexually active women while others endorse delaying Pap smear screening until age 25. STI screening can be accomplished with urine sample

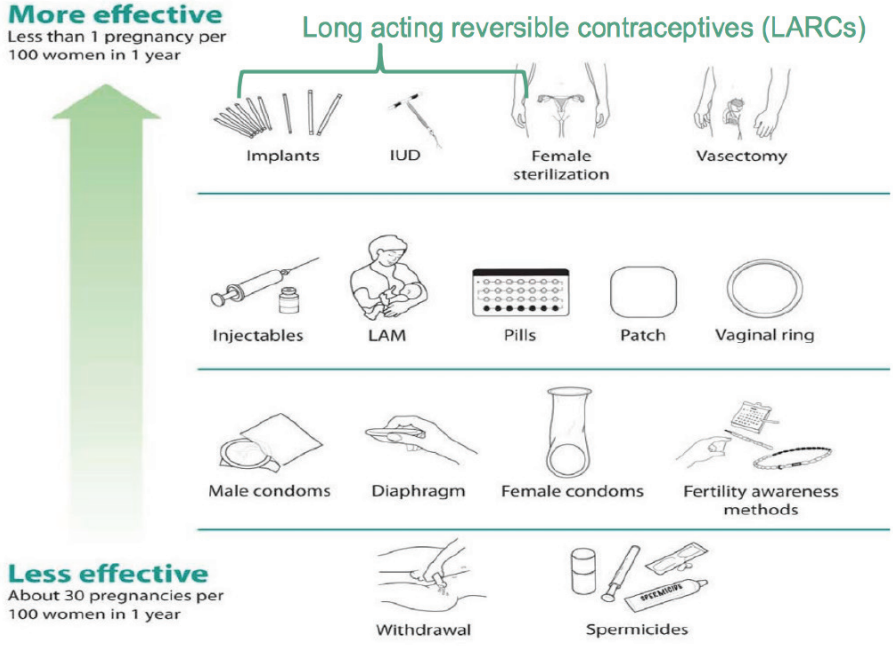

Figure 1. World Health Organization Tiered approach to contraceptive effectiveness

**Adapted from Family Planning: A Global Handbook for Providers (2018 Update) (37)*

IUD: intrauterine device

for polymerase chain reaction, self-collection swabs, or cervical swab collection. STI screening is not a requirement prior to IUC placement. STI screening may be performed on the day of IUC insertion but insertion should not be delayed while waiting for the results, provided that there are no overt signs of infection. HCPs should provide at least a year-long prescription and should consider having samples on site to provide to adolescents (38). All adolescents should be counselled on how long to use back up contraception after starting a new contraceptive method. The Cu-IUD is effective immediately while CHC methods, the single rod implant, the LNG-IUS, and DMPA are effective after seven consecutive days of use. Additional information on what to do if they miss/delay taking their contraceptive method should be provided.

Non-contraceptive Benefits

Counselling on contraceptive options should also include discussion about non-contraceptive benefits. Hormonal methods can provide improvement in heavy menstrual bleeding (HMB) and dysmenorrhea. CHC can also improve cycle regularity, acne, hirsutism, and premenstrual symptoms. Adolescents may prefer concealed options such as injectables, implants or IUC.

Emergency Contraception

Regardless of the contraceptive method they choose, adolescents should be aware of EC and know that it can be used in the setting of contraceptive failure, such as condom interruption, non-adherence to hormonal contraception, or no contraceptive method used. HCPs should write prescriptions for EC, and provide information on how and when to access EC. Hormonal EC is available in many countries without a prescription. Increased availability of hormonal EC does not increase the frequency of unprotected intercourse (UPI), the likelihood of sexual risk-taking, or make women less likely to use effective contraception (48). Available EC options include: LNG-EC, 1.5 mg orally x 1 dose, high dose CHC (Yuzpe method), ulipristal acetate (UPA) (UPA-EC, 30 mg orally x 1 dose), mifepristone (low, mid dose) and insertion of Cu-IUD (25,49). The most effective EC is the Cu-IUD, which can be used up to seven days after UPI provided a pregnancy test is negative. It also has the additional benefit of ongoing contraception; however adolescents may experience barriers accessing a provider within the recommended time window (25,32). Hormonal EC can be offered up to 120 hours after UPI or contraceptive failure, although LNG-EC is more effective the sooner it is taken. UPA-EC may be used up to five days after UPI and may be more effective than LNG-EC in obese adolescents (50). There are no absolute contraindications to EC, aside from pregnancy or previous sensitivity reactions. Use of a Cu-IUD for EC has the same eligibility criteria as routine Cu-IUD insertion (2,41).

LNG-EC, UPA-EC, and mid dose mifepristone are all more effective than the Yuzpe method although all methods have been shown to decrease pregnancy rates (49). The Cu-IUD causes an inflammatory reaction that is toxic to oocytes, spermatozoa, and increases smooth muscle activity in fallopian tubes and myometrium preventing implantation. Hormonal EC works by impairing follicular development of the dominant follicle provided they are taken prior to ovulation. LNG-EC is preferred over the Yuzpe method owing to higher effectiveness - up to 85% if used within 72 hours. UPA-EC is more effective than LNG-EC likely due to its ability to disrupt ovulation even if taken after the LH surge has begun. For adolescents using LNG-EC or the Yuzpe regimen, hormonal contraception can be resumed immediately. In the case of UPA-EC, initiation of hormonal contraception should be delayed for five days due to potential interactions between the two medications that may affect effectiveness and UPA-EC's ability to delay ovulation (51). Backup contraception and/or abstinence should be used until hormonal contraception has been taken for at least seven consecutive days. On the other hand, the Cu-IUD is immediately effective for ongoing contraception. EC users should have a pregnancy test if spontaneous menses do not occur within 21 days of EC use, if the next menstrual period is lighter than usual, or if it is associated with abdominal pain not typical of the woman's usual dysmenorrhea. If a pregnancy occurs in a cycle during which oral EC was taken, the adolescent should be advised that there does not appear to be a harmful effect on pregnancy outcomes and there is no increased risk of congenital abnormality (48).

EC is a useful back-up method for condom use: if the condom breaks, slips, or is not used, there is still a further possibility of preventing pregnancy. However, the efficacy of hormonal EC is significantly lower than regular use of contraception and its preventive efficacy should not be overestimated. In most clinical scenarios, EC provision should be considered an opportunity for counselling and to start a continuous and effective contraceptive method as soon as possible (5). Quick Start is described previously.

Medical Eligibility Criteria for Contraceptive Use in Adolescents

Although age itself is not a contraindication to the use of any method of contraception, reversible contraceptive methods

are generally preferred in adolescents. Guidance for the safety of contraceptive use in women with certain characteristics or medical conditions are provided in the form of MEC from the WHO, the CDC, the Faculty of Sexual and Reproductive Healthcare, and other international organizations (4,17,52). For each medical condition/characteristic, contraceptive methods are placed in one of four categories to determine contraceptive eligibility (Table 4). The WHO and CDC also developed Selective Practice Recommendations for Contraceptive Use that recommend which tests and exams should be performed prior to providing contraception (2,41). Breast, pelvic and genital examination, Pap smears, and bloodwork are not recommended routinely because they do not contribute to increased safety of CHC use. Ideally, blood pressure and body mass index (BMI) should be recorded for adolescents prior to starting CHC but should not delay initiation of contraception. A medical history should be taken to alert HCPs to conditions or risk factors that might be a contraindication to contraceptive use.

Contraceptive Options for Adolescents

Intrauterine Contraception

IUCs are LARC methods that are highly effective and can be used by women of any age. Neither age nor nulliparity are contraindications to their use although rates of IUC expulsion are significantly higher in adolescents compared to older women regardless of parity or IUC type (4,53). Many international societies have stated that IUCs are a safe first line choice for adolescents (8,31,32,38,54,55) and encourage HCPs to counsel all adolescents on their use for the prevention of pregnancy due to their low typical use-failure rates and high one-year continuation rates. IUC rates have a 99% efficacy, with over 80% continuing with the method at one year (54). There are two types of IUCs: Cu-IUD and LNG-IUS. The Cu-IUDs may either have a frame (usually T-shaped) or be frameless and contain a varying amount of copper. The LNG-IUS's (LNG-IUS 20, LNG-IUS 12, LNG-IUS 8) contain different amounts of levonorgestrel in their reservoir. The main mechanism of action of all IUCs is the prevention of fertilization.

Table 4. Medical Eligibility Criteria categories for contraceptive use

Category	Definition of category
1	No restriction on the use of the contraceptive method.
2	The advantages of using the method generally outweigh the theoretical or proven risks. The method can generally be used but more careful follow-up may be required.
3	The theoretical or proven risks usually outweigh the advantages of using the method. Use of the method requires expert clinical judgement and/or referral to a specialist contraceptive provider because use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable.
4	There is an unacceptable health risk and the method should not be used.

Ref. 4,17,41,52

Prior to providing or placing an IUC, absolute and relative contraindications should be reviewed. There is no requirement for pre-placement ultrasound. HCPs may require additional training for insertion. The success rate for insertion in adolescents is 96% (56). Adolescents may choose the LNG-IUS for its non-contraceptive benefits that include a reduction in menstrual bleeding and dysmenorrhea. The LNG-IUS 20 (Mirena®) is approved for treatment of HMB, and may prove beneficial for adolescents with HMB, bleeding disorders, and those on anti-coagulation (57). Although the LNG-IUS has less systemic absorption compared to CHCs, some adolescents experience hormonal side effects including acne, breast tenderness, headaches, and mood changes. Functional ovarian cysts may occur in LNG-IUS users, however these cysts are often asymptomatic and do not require further intervention (54). Adolescents choosing a Cu-IUD may be seeking a LARC method with minimal hormonal exposure. Cu-IUD users may experience increased menstrual blood loss and dysmenorrhea. Adolescents can be offered non-steroidal anti-inflammatory drugs (NSAIDs) and/or tranexaminic acid to help decrease menstrual blood loss and dysmenorrhea. With time, the number of unscheduled bleeding days tends to decrease with both LNG-IUS and Cu-IUD users. Occasionally IUC users may request IUC removal due to ongoing dysmenorrhea.

HCPs should counsel the adolescent about IUC insertion and not rush. Handouts may be helpful and can include information about the need for ongoing condom use to protect against STIs, duration of back-up contraception after insertion (seven days for the LNG-IUS, none required for Cu-IUD), recommendations for prophylactic NSAIDs for insertion, common initial side effects such as cramping or unscheduled bleeding, and when to seek medical assessment. Pre-placement NSAIDs have been shown to reduce discomfort post-insertion. Currently, there is no evidence to support routine pre- and post-placement ultrasound. Although in selected cases vaginal and/or oral misoprostol taken pre-procedure may help with IUC insertion, its routine use should be discouraged due to an increase in side effects such as bleeding, abdominal pain and cramping, fever, and higher pain scores post-IUC

insertion (58). Paracervical blocks may reduce pain with tenaculum placement, but have not been shown to reduce pain with IUC insertion. Smaller diameter LNG-IUS's (LNG-IUS 12, LNG-IUS 8) and Cu-IUDs may be associated with less pain on insertion. Adolescents should be offered IUC placement in the clinician's office, and routine insertion in the operating room should be avoided unless this is the adolescent's preference. Prior to IUC placement, the HCP should rule out the possibility of pregnancy (Table 3).

IUCs are not associated with an increased risk of pelvic inflammatory disease or STI acquisition although there is a small increased risk of pelvic infection seen within 21 days of IUC placement (59). STI screening should be performed in women at high risk of STIs prior to or at the time of insertion but it is not necessary to delay IUC insertion until the results are available. Positive results can be treated while the IUC remains *in situ* (54). Routine antibiotic prophylaxis at the time of IUC placement is not recommended. IUCs can safely be used in adolescents with a history of STI, including human immunodeficiency virus (HIV), although insertion should be delayed if there is evidence of mucopurulent discharge. Immunosuppression is not a contraindication to IUC use (4,8).

IUCs may be safely inserted in the immediate post-abortion and post-partum period (delivery to 48 hours). While there may be a slightly higher expulsion rate (10%), this should not be a barrier to offering placement. Immediate post-placental insertion should not be offered in the setting of chorioamnionitis and/or post-partum hemorrhage.

Progestin-only Contraceptive Options

Progestin-only contraceptives do not contain estrogen and thus may be good options for young women who cannot take estrogen. There are few contraindications to progestin-only methods: current breast cancer (Category 4), breast cancer remission within five years, severe cirrhosis, hepatocellular adenoma, malignant liver tumour, and unexplained vaginal bleeding (Category 3) (4,17,60). Non-contraceptive benefits of progestin-only options include decreased dysmenorrhea and endometriosis-related pain. The most common side effect is unscheduled bleeding. All progestin-only contraceptive options are safe for adolescents, with the implant being a WHO Tier 1 contraceptive method (37).

A) Contraceptive Implant

The single rod implant containing etonogestrel, an active metabolite of desogestrel, is the most effective method of reversible contraception with an efficacy of 99%. It is effective *in situ* for up to three years, although it is likely effective for up to four years, and high continuation rates are seen at one and two years (28,60,61). Its contraceptive effect is due to cervical mucous thickening, thinning of endometrial lining, and ovulation inhibition. The most common side effect is unscheduled bleeding which is variable and does not necessarily improve with time. Implant users requesting removal often cite abnormal uterine bleeding, weight gain, or acne as the reason for removal (62). Functional cysts can be seen in users, but usually do not require further intervention (60). The implant does not have an adverse effect on bone mineral density (BMD) such as that seen with DMPA, likely owing to ongoing ovarian activity that allows for endogenous estradiol to support bone health, but there is limited evidence in adolescents. This Tier 1 method may be a good option for adolescents because it is non-coitally dependent, does not require daily user action, and is discrete. Advantages of this LARC include 3-year duration of effectiveness, reversibility, discretion, and can be used by adolescents who have contraindications to estrogen. It can be seen on X-ray. Contraceptive implants can be inserted post-abortion, and immediately post-partum thereby reducing rapid repeat pregnancy and repeat abortions among adolescents (63).

B) DMPA

DMPA-IM is an intramuscular injection that is administered every 12 weeks by a HCP. A lower dose subcutaneous version (DMPA-SC) that can be self-administered is available in some countries. DMPA inhibits pituitary gonadotropins, leading to anovulation and causes thickening of cervical mucous. Advantages of this method include discretion, infrequent dosing, and non-contraceptive benefits such as reductions in dysmenorrhea, premenstrual symptoms, HMB, fibroids, anemia, seizures, and sickle cell crises (8,60). It is one of the few systemic hormonal contraceptives that can be reliably used with liver-enzyme inducing drugs because its concentrations are not affected (5). Disadvantages may include having to access a HCP for intramuscular injections, unscheduled bleeding, delayed return to fertility, and weight gain. Adolescents using DMPA appear to gain more weight than non-users or users of other contraceptive methods (64). Adolescents who experience more than a 5% weight gain after six months of DMPA use may be at risk of continued excessive weight gain (65). DMPA has high rates of amenorrhea, with up to 68% of DMPA users being amenorrheic at 24 months. Although unscheduled bleeding may decrease in amount and frequency with time, irregular bleeding is a common reason for discontinuation.

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DMPA use can be associated with a reversible BMD loss, likely due to the estrogen deficiency that accompanies its use (66). This may be of concern in adolescence, when bone accrual should be occurring (67,68). The BMD loss associated with DMPA use is greatest in the first one to two years which has led several organizations to recommend a maximum duration of use of two years. The bone loss seen with DMPA use is similar to bone loss seen with pregnancy and appears to return to baseline within two years of discontinuation (69,70). Both the American College of Obstetricians and Gynecologists and the Society of Obstetricians and Gynaecologists of Canada have recognized the risks of unintended pregnancy in adolescents if their contraceptive options are limited and hence have stated that there should no restriction on the use of DMPA or duration of use in women who are otherwise able to use the method (60,71). The WHO has determined that for females younger than 18 years, the advantages of using DMPA generally outweigh the theoretic safety concerns regarding fracture risk (72).

Routine BMD monitoring is not recommended in adolescents using DMPA because dual energy X-ray absorbtiometry has not been validated in these populations. Although studies have demonstrated that low dose estrogen supplementation limits BMD loss in adolescent DMPA users, it isn't recommend because of potential adverse effects and because there is lack of clinical evidence for the prevention of fractures in the adolescent population (71). Adolescent DMPA-users should be counselled on adequate calcium and vitamin D, weight bearing activity, and avoidance of alcohol, caffeine, and smoking which can be associated with BMD loss. HCPs should discuss the overall risks and benefits with DMPA users at regular intervals.

Recently, the WHO reviewed concerns about potential increased HIV acquisition in DMPA users. They determined that for women at high risk of HIV acquisition there are no restrictions for use of reversible methods (73). A recent randomized controlled trial did not find an increased risk of HIV acquisition amongst Cu-IUD, DMPA-IM, or LNG implant users (74).

C) The Progestin-only Pill (POP)

The POP is taken every day, without a HFI. This method works via thickening cervical mucous with anovulation seen in only 50% of user. Adolescents should be counselled that POP needs to be taken at the same time every day to avoid pregnancy risk. It is often used as post-partum contraception when women are breastfeeding. Users may continue to have regular cycles, however, unscheduled bleeding is the most common reason for discontinuation

Combined Hormonal Contraception

CHC methods contain an estrogen and a progestin. They include the pill, patch, and vaginal ring. In the absence of medical contraindications adolescents can safely use CHC. Absolute and relative contraindications should be reviewed prior to initiation (4,17). Common side effects including unscheduled bleeding, nausea, and headaches, should be discussed with the adolescent prior to initiation, as this improves continuation (36). Adolescents and young women can be counselled that they can take the CHC with a 4- or 7-day HFI, and/or can take cyclically or in extended cycle (Skipping periods). Benefits of extended cycle use include reduction in dysmenorrhea, HMB, acne, anemia, and conditions exacerbated by cyclic variations (e.g. migraine without aura, epilepsy, irritable bowel syndrome, inflammatory bowel disease, mood, behaviour) (8,75). Women taking CHC in extended cycle either experience equivalent or less unscheduled bleeding compared to cyclic counterparts (75). Extended/continuous cycles can be achieved by using the hormone for two, three, or more cycles back-to-back, without taking a HFI and having a withdrawal bleed. The safety of this approach is well established and adolescents should be counselled that not experiencing bleeding during a HFI is safe, as evidenced by equivalent endometrial assessment via ultrasound and/or endometrial biopsy (75). For contraceptive efficacy, a HFI should not be taken until at least 21 consecutive days of hormonal contraception has been used. It is helpful to provide adolescents with written instructions or website links on how to take CHC in extended cycle, and what to do if a dosage is missed. Follow-up should be scheduled at one and three months to ensure the method is acceptable and to assess side effects.

A. Combined Oral Contraceptive (COC) pills are the most popular hormonal contraceptives among adolescents. Typical use failure rate is 9% (12) and is usually secondary to non-adherence. Adolescents should be counselled on behaviours to increase contraceptive adherence including: regular schedule, phone alarm, and family member support (8,9). Adolescents should be provided with resources (paper, app, online) to assist when pills are missed.

B. The Contraceptive Patch should be placed on the buttocks, upper arm, upper torso, or abdomen once weekly for three weeks. During the HFI in the fourth week, a withdrawal bleed usually occurs. In obese adolescents, there may be a slightly higher risk of failure with the patch (76) but obesity is not a contraindication to use of the contraceptive patch (4,17). It can be used continuously for menstrual suppression if desired.

C. The Vaginal Contraceptive Ring is inserted into the vagina by the adolescent and should remain in the vagina for three weeks (21 days), although pharmacokinetic data indicate that it is effective for at least 28 days (77). When the ring is removed, the adolescent can choose to have a 4- to 7-day HFI or she can insert a new ring immediately to avoid having a withdrawal bleed. At no time should the HFI exceed seven days. The ring can stay in the vagina during sexual intercourse but if the adolescent does wish to remove it during intercourse, it should not remain out of the vagina for more than three hours (42).

Considerations with Combined Hormonal Contraceptive

i. Weight gain: A Cochrane review did not find a significant association between COC or transdermal CHC and weight gain (78). There is currently insufficient evidence to link CHC use with weight gain. When counselling adolescents about weight gain, it is important to discuss ongoing physical development, and average weight changes for women over a year.

ii. Mood: Data on CHC effect on mood is conflicting. Placebo-controlled trials have not demonstrated a significantly increased risk of mood changes in CHC users compared with placebo users, and there is some evidence that COCs are protective for mood (79). COC's containing drosperinone are associated with an improvement in premenstrual dysphoric disorder symptoms (80). Conversely, a large Danish prospective cohort study found an increased risk for first use of an antidepressant and first diagnosis of depression among users of different types of hormonal contraception, with the highest rates among adolescents (81). HCPs should counsel adolescents that CHC may be associated with mood changes, but there is no conclusive evidence linking CHC to depression (32).

iii. Venous thromboembolism (VTE): The baseline risk of VTE in adolescents is very low (1 per 10,000). CHC use is associated with a 3-fold increase risk for VTE with an absolute risk of 3-4 per 10,000 in adolescents. There currently is inadequate data to support preferential prescribing related to increased VTE risk based on type of progestin or dose of ethinyl estradiol (82). Prospective cohort studies do not seem to show a significant difference in VTE risk by progestin type (83,84). Routine thrombophilia screening in adolescents prior to initiating CHC is not advised.

iv. BMD: Adolescence is a time of bone mass accrual which continues up to approximately age 25 years (38). Although data on CHC effects on BMD is conflicting, there is currently no evidence supporting increased risks of osteoporosis or fracture in CHC users (72,85). Early data has suggested that in healthy adolescents, COCs with at least 30 mcg ethinyl estradiol may be preferred due to poorer bone mineralization seen with lower dose options (38), and that extended regimens may be preferred to 28-day cyclic regimens because there is greater bone accrual (86). Adolescents with eating disorders are at risk for decreased BMD. Although a recent study suggested COC use was associated with normalization of bone resorption markers in adolescents with anorexia nervosa and may limit bone loss (87), CHCs are generally not recommended for prevention of osteoporosis in this population (32).

v. Obesity: There are no contraindications to CHC use based on body weight and/or BMI alone (17,42). Studies demonstrate either equivalent or increased pregnancy rates among obese CHC users, however more high quality studies are needed (88).

Barrier Contraception

Male condoms are the most commonly used contraceptive method at first intercourse, and one of the most commonly used methods among adolescents (9). This method retains its popularity due to its low costs and lack of need for a prescription. Typical use failure rates are as high as 18% and may be higher in adolescents due to inconsistent/incorrect use (8,89). HCPs can help ensure that adolescents understand proper condom use including sizing, placement, storage, and safe lubricants as well as how to negotiate condom use with their partners (32,89). There are concerns that adolescents choosing LARCs have the lowest rates of dual method use (90). Regardless of the contraceptive method chosen, HCPs should encourage adolescents to continue to use condoms for STI prevention as well as contraceptive back-up in the event of a contraceptive failure and/or non-use.

Conclusion

The ability to freely choose when and how many children to have is a basic human right. Contraception is an important pillar for the prevention of unintended pregnancy in adolescents. HCPs should strive to provide care within the human rights based framework and to work with adolescents to find a method that best meets their personal biopsychosocial needs and that they will be able to adhere to. Adolescents should have access to a wide range of contraceptive options with LARCs being first line options due to their greater effectiveness. However, as LARC uptake increases among adolescents, it is important to incorporate messages about condom use specifically for STI prevention.

Healthcare providers must provide counselling that is appropriate to the adolescent, acknowledges how they access health care, and is not perceived as directive or coercive.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Nicole Todd, Amanda Black, Concept: Nicole Todd, Amanda Black, Design: Nicole Todd, Amanda Black, Data Collection or Processing: Nicole Todd, Amanda Black, Analysis or Interpretation: Nicole Todd, Amanda Black, Literature Search: Nicole Todd, Amanda Black, Writing: Nicole Todd, Amanda Black.

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Management of Menstrual and Gynecologic Concerns in Girls with Special Needs

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Abstract

For girls with physical and developmental disabilities and their families/caregivers, puberty and menstruation can present significant problems such as vulnerability, abuse risk, unintended pregnancies, difficulties with managing menstrual hygiene, abnormal uterine bleeding, dysmenorrhea, behavioral difficulties/mood concerns or changes in seizure pattern. Healthcare providers may have an important and positive impact for both the adolescents and their families/caregivers during this stage of life. Whether menstrual manipulation is indicated should be decided after a detailed history is taken from both the patient and the caregivers to determine the impact of current problems on quality of life. It should be explained that complete amenorrhea is difficult to achieve and realistic expectations should be addressed. The goals for the management of menstrual concerns should be a reduction in the amount and total days of menstrual flow, reduction of menstrual pain and suppression of ovulatory or cyclic symptoms, depending on each individual patient's needs. Advantages and disadvantages of available treatment methods should also be discussed.

Keywords: Adolescent, developmental disabilities, menstruation

Introduction

Adolescence, the period of transition between childhood and adulthood, can cause many difficulties for developmentally delayed adolescents and their families/caregivers due to hormonal changes, which result in menstruation and other reproductive health issues. These patients are also at high risk of sexual abuse and unwanted pregnancies (1). With the onset of pubertal changes, adolescents and the families start to have concerns about menstruation although most are able to manage these menstrual periods well without any intervention (2,3). Therefore prepubertal counselling is important but it should be noted that any intervention should be postponed until menarche, since it may affect the natural growth pattern of the adolescent and may compromise the diagnosis of genital tract malformations or reproductive endocrine pathologies (4). For most adolescents with developmental delay growth progresses according to normal growth curves, however precocious puberty may occur in cerebral palsy patients (5).

Gynecologic Assessment

Communication with these adolescents may vary in effectiveness due to their mental status, hearing and communication function. Clinicians may need to communicate with them either with simple language or with illustrations. In addition writing, sign language or a translator may be useful or even a necessity.

The biggest assumption is to consider these patients as asexual. These adolescents usually have similar sexual thoughts, feelings and in some cases experiences as their peers. Therefore questions concerning sexuality and risky behavior should be asked of these patients, preferably alone, and the confidentiality of the dialogue should be established (6). History should be taken according to current symptoms, main concerns and expectations from treatment. The impact of menstrual cycles on the health and hygiene of the adolescent should be discussed. Counseling should be given to both the adolescent and the family/caregiver regarding sexuality, sexual abuse, problems concerning menstrual cycles, contraception and need for menstrual suppression.

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Since it is now advised to start taking the Papanicolaou (PAP)-smears after the age of 21 and sexually transmitted diseases can be screened with non-invasive tests, gynecologic examinations are now needed less (7). For inspection of the external genitalia, a "frog-leg" position is usually preferred. If the abduction of the legs is compromised, the patient should lie on one side and the legs may be elevated for the inspection. When gynecologic examination is indicated but cannot be performed due to lack of communication or lack of mobility, it should be carried out under sedation or general anesthesia. When a PAP-smear test is indicated but a speculum examination cannot be performed, the PAP-smear may be taken with palpation of the cervix and by guidance using the fingers. HPV vaccination is strongly advised for these patients between the ages of 9-26 (8).

Sexual Education and Prevention of Sexual Abuse

Parents/caregivers of adolescents with special needs are often worried that their children constitute a high risk group for sexual abuse and unwanted pregnancies (1). These patients may not be able to differentiate between good intentioned acts of help and inappropriate behavior, since they are used to getting help for daily activities. In addition, since these patients are often considered asexual, they do not receive the same degree of counseling on these important topics as their peers. Thus it becomes the task of the clinician to provide additional, appropriate and sufficient sexual education for this group, as part of general health services, listen to the concerns of the families and consult with them on how to educate their children in these matters.

The healthcare provider should determine if an adolescent is safe and if he/she is capable of giving consent to any sexual activity. This requires an assessment of his/her level of understanding on these matters. Behavioral changes such as regression, social withdrawal or self-harm can be an indicator of abuse for these patients. Also during physical examination, pain and bruises in unexpected areas of the body and genital complaints such as discharge or pruritus should be considered as alarming signs (9). It is especially important that patients of age 12-14 years and older should be examined in complete privacy, if communication between the clinician and the patient can be established.

Sexual education should start by explaining basic aspects of sexuality, including anatomical features of both genders, and defining appropriate and inappropriate behaviors in both public and private places. The education should be continued with topics including sexuality, pregnancy, contraception and sexually transmitted diseases. A key subject in this education should be prevention of sexual abuse. Depending on the level of understanding of the patient, a basic education of NO-GO-TELL strategy must be given (9). This strategy teaches the adolescent to say "No" if he/she is not comfortable, to get away from that situation and to tell someone he/she trusts about what has happened.

Menstrual Concerns

Menstruation can cause significant challenges to these adolescents and their families/caregivers. These problems include personal hygiene, irregular or heavy bleeding that is usually seen within 2-5 years of menarche, dysmenorrhea, mood swings, and medical problems exacerbated by menstrual cycle, such as menstrual migraine or catamenial epilepsy. Additionally, sexual abuse and unwanted pregnancies are also crucial concerns at this stage.

Menstrual Manipulation

A detailed history taken from both the patient and the caregivers, including the problems caused by menstruation and its impact on quality of life, should be the first step in management. As in normal practice with the general population, any other factors causing these complaints should be ruled out (10). Some of the conditions that may cause menstrual disorders in this group of patient include increased incidence of hypothyroidism in Down Syndrome, drug-induced hyperprolactinemia in patients receiving antipsychotic medication, and increased frequency of polycystic ovary syndrome in epilepsy patients (11,12).

After determining the extent and cause of menstrual problems, clinicians should decide if menstrual manipulation is indicated and the possible treatment options, advantages and disadvantages of the available options and possible clinical outcomes of these treatments, all of which should be discussed with the patient and the family (Table 1). It should be explained that complete amenorrhea is difficult to achieve and realistic expectations should be explained. The clinical aim of menstrual suppression is to shorten the time of bleeding and decrease the menstrual flow (13).

Nonsteroidal anti-inflammatory drugs: Nonsteroidal anti-inflammatory drugs (NSAIDs), when used according the patients weight, may decrease menstrual bleeding volume by up to 30-40% in ovulatory cycles (14,15). This treatment option may be preferred in the management of heavy menstrual bleeding and dysmenorrhea.

Estrogen containing treatment options: Combined oral contraceptives (COCs) can be used continuously for menstrual suppression. This treatment achieves up to

50% amenorrhea, although spotting is commonly seen, especially at the beginning of the treatment. Tablets can be powdered if they cannot be swallowed whole, although they are generally small in size. In the general population, the risk of venous thromboembolism (VTE) for adolescents and young women is very low. Use of COCs doubles the risk, but the risk of VTE remains quite low in this age group (16). Combined contraceptives may also be used in the forms of dermal patch or vaginal ring. Even though patches are more effective in increasing blood estrogen concentrations, there is insufficient evidence to demonstrate whether this may lead to an increased risk of VTE or not. Still, it is considered logical not to offer this treatment option in immobilized patients (17). In addition the vaginal ring is not a suitable option for patients with restricted mobility.

Data concerning the usage of estrogen-containing methods in patients with restricted mobility or who are immobilized and its relationship with VTE are inconclusive. However, it should be noted that third generation COCs are associated with higher risks of VTE and thus are not advisable as first line therapy for these patients (18,19).

Progestin-only Treatment Options

1. Oral progesterone: Cyclic use of progesterone can decrease the amount of bleeding in anovulatory cycles (20). In addition, daily progesterone use, including progestin-only oral contraceptives, can be used for menstrual suppression. Though amenorrhea achievement rates are low, its efficacy is also closely related to regular use.

2. Depot medroxyprogesterone acetate (DMPA): Amenorrhea can be achieved in approximately 90% of patients following the fourth dose of intramuscular DMPA injection, used at intervals of ninety days. Spotting may be seen, especially in the first three months. The biggest concern about this medication is the loss of bone mineral density and risk of fracture. However, this effect is transient and bone mineral density increases again upon discontinuation of the medication and routine follow-up of bone mineral density is not recommended in these patients, but adequate intake of calcium and vitamin D should be encouraged (21). Developmentally delayed adolescents are already predisposed to poor bone health, due to anticonvulsant medication use, reduced mobility, and undernourishment. In adolescents, if DMPA is the method of choice for menstrual suppression, it is important to re-evaluate whether to continue treatment yearly and to discuss the risks and benefits with patients and families prior to starting therapy and regularly thereafter at follow-up appointments (22,23).

A further concern with the use of DMPA is weight gain. Especially in the immobile population, even a small weight gain can impact negatively on independent functioning of the patient. Therefore changes in weight in patients using DMPA should be carefully monitored.

Table 1. Treatment methods and their advantages and disadvantages

Treatment	Specific advantages	Concerns regarding the treatment
NSAIDs	- Reduced flow and pain	- Gastrointestinal problems
COCs	- Can be used as extended or continuous	- Increased risk of VTE in immobilized patients? - Need to take daily medication - Drug interactions with some anti-epileptic drugs
Patch	- Weekly use - Can be used as extended or continuous	- Increased risk of VTE in immobilized patients? - Drug interactions with some anti-epileptic drugs - The patches can be removed by the patients
Vaginal ring	- Monthly use - Can be used as extended or continuous	- Increased risk of VTE in immobilized patients? - Drug interactions with some anti-epileptic drugs - Placement may need assistance
Oral progestins	- Decreased flow	- Breakthrough bleedings - Need to take daily medication - Drug interactions with some anti-epileptic drugs
DMPA	- Injection once every three months - High amenorrhea achievement	- Weight gain - Bone mineral density loss
Levonorgestrel releasing IUD	- Insertion once every 3-5 years - High amenorrhea achievement	- Need for general anesthesia for insertion - Breakthrough bleeding

NSAIDs: nonsteroidal anti-inflammatory drugs, COCs: combined oral contraceptives, VTE: venous thromboembolism, DMPA: depot medroxyprogesterone acetate, IUD: intrauterine device

3. Progesterone-releasing intrauterine device (IUD): Even though spotting is often seen during the first months following insertion, amenorrhea achievement rates are high with this treatment option over the long term. Progesterone-releasing IUDs reduce menstrual flow and dysmenorrhea, even if amenorrhea is not achieved. Amenorrhea rates are higher with IUDs containing 52 mg levenorgestrel and its efficacy continues for around five years. Usually the insertion is performed under sedation or general anesthesia due to communication problems and mobility restrictions. Several studies investigating the use of progesterone-releasing IUDs in adolescents with developmental disability have reported amenorrhea rates of up to 70% and low expulsion rates and removal rates due to bleeding or pain (4,24,25,26).

Other treatment options: Subcutaneous implants are not suggested as first line therapy since it usually causes irregular bleeding and the amenorrhea rate is only about 20% (8,27). It is also a disadvantage that the insertion and removal will most likely need to be done under anesthesia. Endometrial ablation is also not recommended as a first line therapy, since there are no data on its use in adolescents and the amenorrhea rates are low in a young population. Even though some families request hysterectomy, since it is an irreversible technique with possible surgical risks and complications, it is not recommended unless there are additional medical indications present.

Premenarchal intervention is not suggested, since it may affect the natural growth pattern of the adolescent and may compromise the diagnosis of genital tract malformations or reproductive endocrine pathologies (4). It should also be remembered that most of these adolescents will tolerate menstruation well (4,9).

Menstrual Mood Disorders

Premenstrual syndrome (PMS) is defined as the emotional and physical symptoms that are only seen in the luteal phase of the menstrual cycle (28). Although there is not enough data about the incidence of PMS among developmentally delayed adolescents, PMS has been reported in approximately 18% of adults with developmental delay (29). Most of these cases have shown a response with pain medication, suggesting that dysmenorrhea may be the cause of these menstrual mood disorders, especially in a population that cannot communicate easily. Diagnosis may be made by showing that these symptoms are cyclic and persist for at least 2-3 months. The first treatment option is NSAIDs. In cases with no response to NSAIDs, hormonal suppression with COCs, especially those containing drospirenone 3 mg/ethinyl estradiol 20 µg (24/4 regimen), or DMPA is widely used for the treatment of PMS. As an alternative option, or an additional approach for cases resistant to the first and second line therapies, selective serotonin reuptake inhibitors may also be used (30,31).

Problems Concerning Epiletic Adolescents

Epilepsy is seen in nearly 10-20% of patients with cognitive disabilities and 30% of them have catamenial epilepsy. Catamenial epilepsy is defined as the epileptic seizure that occurs during menstruation or change in seizure frequency according to the menstrual cycle. Seizure frequency may increase during three phases. These are the periovulatory phase, the premenstrual phase or the luteal phase, when progesterone levels remains low in anovulatory patients. The increased frequency of seizures is related with increased estrogen/progesterone ratios. Estrogen acts as a proconvulsant whereas progesterone increases the seizure threshold. Although the data is inconclusive, progesterone use in the luteal phase or DMPA use has been shown to decrease seizure frequency in these patients (32). Also use of continuous COCs is thought to decrease the frequency of the seizures by achieving amenorrhea, but again there is inadequate data to reach a robust conclusion.

Some antiepileptic drugs may decrease the efficacy of hormonal methods by affecting with hepatic cytochrome p450 (33). In the presence of persistent breakthrough bleeding, the dosage of estrogen/progesterone should be increased or DMPA should be injected on a more frequent basis. Blood concentrations of Lamotrigine may be lower in patients using COCs, therefore monitoring should occur and doses should be adjusted accordingly (33).

Conclusion

Puberty and menstruation is often complex for girls with physical and developmental disabilities and their families/caregivers. While premenarcheal counseling provides great benefits in the management of these patients, no intervention or medical treatment is recommended during this period. Menstrual problems affecting quality of life in post-menarche period can be managed successfully by using various hormonal methods. A clear explanation of the realistic expectations from the treatment and the advantages and disadvantages of the existing methods increase the success and continuity of the treatment.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Süleyman Engin Akhan, Design: Süleyman Engin Akhan, Literature Search: İnci Sema Taş, Writing: Özlem Dural.

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Hormone Replacement Therapy in a Patient with Hypogonadism and Coexisting Medical Conditions

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Abstract

In adolescents and young women, there is limited data on the type of replacement, route of administration, and ideal doses to be used in systemic hormone therapy administered for the treatment of hypogonadism. In particular, management of patients with complicated systemic diseases or at risk of thrombophilia may present significant challenges. We present a case of a 15-year-old adolescent girl with hypogonadism and coexisting medical conditions, who was evaluated for systemic hormone therapy.
Keywords: Adolescent, hypogonadism, hormone replacement therapy

Introduction

Systemic hormone therapy in adolescents and young women with hypogonadism is an effective treatment for the symptoms of hypoestrogenism, thus reducing long-term health risks. Oral or transdermal hormone replacement therapy (HRT) that provides the physiological hormone levels required for this age group is considered as a first-line approach, although combined oral contraceptives (COCs) can be also used for estrogen replacement (1,2). We report a 15 year-old girl diagnosed with hypogonadotropic hypogonadism, who also had obesity, dyslipidemia, factor V Leiden mutation and a history of renal transplantation. We present this case with the aim of discussing the approach and appropriate treatment in terms of systemic hormone therapy.

Case Report

A 15.3 year-old girl presented with short stature and primary amenorrhea. She had normal birth weight at 40 weeks of gestation. She had chronic renal failure due to nephrotic syndrome since the age of two years and had renal transplantation two years prior to this presentation. She was on glucocorticoid and immunosuppressive drugs (micofenolat, mofetil and tacrolimus) and was on enalapril for hypertension. Her parents were unrelated and family history was unremarkable.

On physical examination, her weight was 46.6 kg [1.6 standard deviation score (SDS)] and height 129.4 cm (-5.5 SDS) and body mass index was 27.7 kg/m^2 (2.1 SDS). She had central obesity, a dorsocervical fat pad, hirsutism and striae. Her blood pressure was 110/80 mmHg. The rest of the physical examination was normal. She had undergone normal puberty without menarche and breast and pubic hair were at Tanner stage 5.

Laboratory tests including complete blood count, glucose, electrolytes, calcium profile, prothrombin time, activated partial thromboplastin time, renal and liver function tests were within normal range. She had dyslipidemia (total cholesterol = 248 mg/dL, low-density lipoprotein cholesterol = 168 mg/dL). Other laboratory results were normal, including thyroid function tests, prolactin concentration, parathyroid hormone and 25-hydroxy vitamin D (Table 1). She had osteoporosis on dual energy X-ray absorbtiometry (DXA; L1-L4 Z score-2).

She had low luteinizing hormone, follicle-stimulating hormone and estradiol concentrations (Table 1). Pelvic ultrasound was normal (right ovary volume 7 mL, left ovary volume 7.2 mL with normal echogenicity and uterus volume 49.2 mL). Thrombophilia investigation of the patient

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Table 1. Hormone analysis of the patient	
LH (mIU/mL) (NR: 0.4-11.7)	0.1
FSH (mIU/mL) (NR: 1.8-11.5)	0.44
Estradiol pg/mL (NR: 34-170)	5
Thyroid stimulating hormone (mIU/mL) (NR: 0.5-4.8)	0.96
Free thyroxine (pmol/L) (NR: 11-22)	15
Prolactin (ng/mL) (NR: 3-24)	9
Parathyroid hormone (pg/mL) (NR: 10-65)	49
25-hydroxy vitamin D (ng/mL) (NR: 30-100)	33

LH: luteinizing hormone, FSH: follicle-stimulating hormone, NR: normal range

showed a heterozygous factor V Leiden mutation. Other investigations for thrombophilia were within normal ranges. Final diagnoses of this patient with kidney transplant were pubertal arrest, hypogonadotrophic hypogonadism, obesity, dyslipidemia, osteoporosis and factor V Leiden heterozygous mutation.

There are some clinical risks evident for the management of this patient. The patient would need HRT for hypogonadism and osteoporosis but had an increased risk of thromboembolism due to the co-existence of factor V Leiden heterozygous mutation and obesity. Thus tailoring the HRT therapy, including the product, dose and route of administration in this patient to avoid some side effects of treatment, was needed. Taking into consideration the existing medical conditions and the increased risk of thromboembolism, she was started on transdermal estrogen treatment (100 micrograms 17 beta estradiol daily) with cyclic oral progesterone replacement (10 mg dydrogesterone for the first 12 days of each month). No side effects or complications were encountered during the first year of treatment.

Discussion

The purpose of estrogen replacement in adolescent and young women with hypogonadism is both to treat the symptoms of hypoestrogenism and to mitigate long term health risks, such as osteoporosis and cardiovascular disease. Although the data on optimal HRT for these patients are limited, hormone replacement (either orally or transdermally) that provides the physiological hormone levels required for this age group should be the first choice treatment (1,2). Estrogen replacement can be also achieved with COCs. However, COCs contain ethinyl estradiol, a synthetic estrogen that is more potent than 17 beta estradiol included in HRT preparations. In addition, they contain higher dose progestins, which maintain primary contraceptive activity. Therefore, they provide more steroid hormone than is needed for physiologic replacement, with unfavourable adverse effects on lipid profile, blood pressure and on haemostatic factors (3) and, at the same time, the effect on bone density is less favorable compared with HRT (4,5,6). For these reasons, HRT is preferrable to COCs for the treatment of hypogonadism compare; HRT is considered the first choice.

The most commonly used estrogen preparations for HRT and recommended dosages are 2 mg oral or 100 micrograms transdermal 17 beta estradiol daily (1,2). To prevent the development of endometrial pathologies in patients with intact uterus, estrogen replacement should be combined with the appropriate dose of progestins. There is also a lack of evidence on the effect of various progestogen preparations in HRT for reproductive age women and adolescents with hypogonadism. However, evidence from postmenopausal women appears to favor micronized natural progesterone due to a better cardiovascular profile and possible risk reduction in breast cancer (7,8). For effective endometrial protection, 10 mg medroxyprogesterone acetate or 200 mg micronized oral progesterone for a minimum of 10 to 12 days per month is required in sequential treatments (9).

Primary or secondary amenorrhea associated with hypoestrogenism affects the acquisition and maintenance of peak bone mass in young women and it is associated with both the degree and duration of estrogen-deficiency (10,11,12). In contrast to postmenopausal women, low bone mass in these young patients is managed most appropriately with HRT instead of antiresorptive drugs such as bisphosphonates (1). Although COCs are sometimes used for estrogen replacement in women with hypogonadism, it has been shown that HRT is superior to COC in increasing bone density at the lumbar spine in women with premature ovarian insufficiency or functional hypothalamic amenorrhea (4,5,6). Compared to the oral route, the transdermal administration of estrogen provides higher and more consistent plasma levels of estradiol, and also does not have a negative effect on serum insulin-like growth factor-1 level, due to avoidance of the 'first past' effects on the liver (13,14). Therefore, transdermal administration may be preferable for HRT in women with severe osteoporosis. In addition, transdermal HRT also appears to have a beneficial effect on serum lipid profiles, inflammatory markers, and blood pressure (15).

Oral estrogen therapy is associated with an increased risk of venous thromboembolism (VTE) because of its effect on the balance between procoagulant factors and antithrombotic mechanisms (16). Since estrogen replacement doses provided in HRT are less potent than estrogen in COC, HRT is expected to carry a lower risk

of VTE. Current evidence of VTE risk in HRT users with menopause at a regular age has shown an increased risk (16). Although there is no data on HRT use and VTE risk in adolescents and young adults with hypogonadism, given that increased age is an important risk factor for VTE, there is an assumption that increase in VTE risk associated with HRT use will be lower than in the postmenopausal population. To further reduce the risk of VTE with HRT, the transdermal route should be recommended for elimination of the 'first past' effects on the liver. Even in studies on HRT users with menopause at the expected age, increased risk of thrombosis has not been shown with transdermal estrogen replacement. In addition, transdermal estrogen does not confer an additional risk in women who carry a prothrombotic mutation (17,18,19). Therefore, transdermal estrogen replacement appears to be a reasonable approach in young women, who have hypogonadism but are at risk of VTE, including patients carrying a prothrombotic mutation. In terms of progestogens used in hormone replacement and VTE risk, no risk increase was shown with the use of micronized progesterone and pregnane derivatives, such as dydrogesterone, medroxyprogesterone acetate and cyproterone acetate, while studies showing an increased in risk with the use of norpregnane derivatives, such as nomegestrol acetate or promegestone, are available (17,19).

In our case, a 15 year-old girl with renal transplant, obesity, dyslipidemia, factor V Leiden mutation, osteoporosis and hypogonadotropic hypogonadism was evaluated for HRT. Factor V Leiden mutation is one of the two most common genetic defects associated with an increased risk of VTE and leads to a 4-5-fold increase in VTE risk (20,21). Taking into consideration the existing medical conditions and the increased risk of VTE in our patient, it was decided to initiate transdermal estrogen treatment with cyclic oral dydrogesterone. Again, there is little evidence concerning endometrial protection in adolescents and young adults, but dydrogesterone appears to be a safe progestogen with an acceptable metabolic profile, similar to micronized progesterone (22).

In contrast to the mild increase in VTE risk present in our patient, patients with hypogonadism but at high-risk of VTE, including patients with high-risk prothrombotic mutations such as homozygous factor V Leiden mutation or antithrombin-3 deficiency, may still benefit from HRT. In the management of such patients, it seems prudent to consult with a hematologist before starting HRT, since prophylactic anticoagulation therapy may be required.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Şükran Poyrazoğlu, Concept: Şükran Poyrazoğlu, Design: Şükran Poyrazoğlu, Data Collection or Processing: Özlem Dural, Analysis or Interpretation: Özlem Dural, Literature Search: Özlem Dural, Writing: Özlem Dural.

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Conservative Management of Vaginal Hypoplasia

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Abstract

In patients with Mayer-Rokitansky-Küster-Hauser syndrome and complete androgen insensitivity syndrome (CAIS), management of vaginal hypoplasia includes non-surgical or surgical vaginal elongation techniques. For these patients, primary vaginal dilation is considered a first-line option to avoid the risks of having surgery and complications that may occur due to these procedures. Non-surgical dilation is a highly successful treatment if treatment is initiated when the patient is emotionally mature and ready. Here, we present a case of CAIS with vaginal hypoplasia managed successfully with non-surgical dilation therapy.

Keywords: Adolescent, Müllerian aplasia, androgen-insensitivity syndrome

Introduction

Non-surgical self-dilation treatments should be the primary approach for the management of vaginal hypoplasia in women with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome and complete androgen insensitivity syndrome (CAIS). Primary vaginal dilation has also been considered as a first-line treatment by the American College of Obstetricians and Gynecologists, because it has a high success rate and has a significantly lower complication risk and much lower cost than surgical vaginoplasty techniques (1,2,3,4,5). Patients should be informed that when they are motivated and ready, most of them (90-96%) will be able to achieve anatomic and functional success with primary vaginal dilation (5). Surgical treatments should be reserved for the rare patient who refuses or fails with dilation therapy. We report an 18 year-old patient with CAIS, who wanted to engage in sexual activity and was referred to the gynecology clinic for the management of vaginal hypoplasia.

Case Report

A 7 year 2 month old girl was referred to the endocrinology clinic for evaluation of testicle-like masses observed in hernia sacs during a hernioplasty operation. She was born at term with a birth weight of 3600 g, with female external genitalia and was raised as a girl. Her parents were first degree cousins but family history was otherwise unremarkable. There was no family history of disorder of sex diferentiation. Bilateral inguinal hernias were noted at 15 months of age. Histopathological findings of a gonadal biopsy reported immature testis tissue.

On physical examination at her first endocrinology visit, her weight was 26.4 kg [0.7 standard deviation scores (SDS)], and height was 126.2 cm (0.8 SDS). Physical examination was normal. Gonads were palpable in the inguinal canals bilaterally. Pubic hair and breast development were both at Tanner stage 1. No virilization symptoms were observed.

Karyotype analysis was 46,XY. Hormone analysis at the age of 21 months showed elevated luteinizing hormone and normal follicle stimulating hormone, estradiol and testosterone concentrations. She had normal testosterone response to human chorionic gonadotropin (hCG) stimulation test. Anti-Müllerian hormone was also within the normal range for male infants (Table 1). Ultrasonography of the pelvis showed no uterus, fallopian tubes, or ovaries. Based on her physical exam and biochemical findings, she was assigned a clinical diagnosis of CAIS. Genetic analysis of the androgen receptor gene was performed, and a hemizygous mutation (c.2668G > A, p.Val890Met) was identified in exon 8.

She underwent regular tumor surveillance throughout childhood, including physical examinations, measurement

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Table 1. Hormone analysis of the patient		
LH (mIU/mL) (NR: 0.02-0.3)	0.373	
FSH (mIU/mL) (NR: 0.26-3)	2.95	
Estradiol (pg/mL) (NR < 15)	11.1	
Anti-Müllerian hormone (ng/mL) (NR: 7.4-243)	53	
hCG test	Basal	Response to hCG
Total testosterone (ng/mL) (NR: 0.025-0.1)	0.08	6.12

hCG: human chorionic gonadotropin, LH: luteinizing hormone, FSH: follicle stimulating hormone, NR: normal range

of α-fetoprotein and hCG, and testicular ultrasound examinations. Breast development started (Tanner stage 2) at age 9 years 10 months, while pubic hair was at Tanner stage 1.

At age 14 years 8 months, her weight was 47.3 kg (-1.2 SDS), height was 160 cm (-0.2 SDS). Physical examination revealed normal female external genitalia and breast development (Tanner stage 5) with sparse pubic hair (Tanner stage 2) and axillary hair. Bilateral gonadectomy was performed at age 14 years 9 months due to the presence of inguinal testes and increased potential risk for the development of a germ cell tumor. Histological analysis of the excised gonads revealed that they consisted of testicular tissue, characterized by immature seminiferous tubules. Estrogen replacement therapy was initiated with transdermal 17 β estradiaol starting at a dose of 50 μg and increasing to 100 μg over a period of one year.

At the age of 18 years she was referred to the outpatient pediatric gynecology clinic for the management of vaginal hypoplasia because she wanted to become sexually active. Physical examination revealed normal breast development, normal female external genitalia, an unformed hymen and blind vaginal pouch with a length of about 3 cm. Pubic hair and breast development were at Tanner stage 2 and 5, respectively.

Since she was emotionally and physically ready to begin primary vaginal dilation treatment, her external genital anatomy was reviewed with the patient, following a detailed explanation of all the stages of the treatment. She was instructed how to use Pyrex tubes of gradually increasing size and diameter and seen in clinic every two weeks. Anatomical success with a 6 cm long vagina was achieved after a clinical follow-up of approximately two months. No complications or adverse effects were encountered during the treatment. She was informed that she would need to continue dilation 2-3 times per week until she began to have regular penetrative intercourse. We also reviewed the methods to decrease sexually transmitted infections, including the use of condoms and the human papilloma virus (HPV) vaccine was recommended.

Discussion

Frank's Method involves the use of vaginal dilators, which increase in size and diameter over time, to stretch a short vagina to a larger length and diameter (6). Although it is a highly effective therapy, many reproductive health providers have little experience of how to guide patients through this process. Dilator therapy should only be suggested to women with high motivation, for example those in a current relationship or those who want to engage in sexual activity. Patients over 18 years of age at the start of treatment have significantly higher anatomic success rates, possibly related to motivational reasons (1). It should be noted that initial vaginal length, even when the vagina appears as a dimple below the urethra, is not associated with anatomical or functional success, but may be associated with duration of dilator therapy. Although there is no difference in anatomic success rates, patients with CAIS have a larger starting vaginal length than patients with MRKH syndrome (7).

Initially, a thorough examination of the external genital anatomy of the patient should be performed with the aid of a mirror and the patient should be able to understand and show the appropriate location and angle for inserting the dilator. She should be instructed to place a small dilator on the distal vaginal apex in a downward angle 1-3 times per day for 10-30 minutes. The patient should be followed up at the clinic at least every two weeks and the length and width of the dilators given should be progressively increased. There is no vaginal length or width specified to begin penetrative intercourse as even elongation by gentle vaginal intercourse alone can be successful with a supportive partner (8,9). Although success has been described anatomically by obtaining a vagina of 6 cm or longer (1), the best definition of success is a functional vagina that is sufficient for comfortable sexual activity reported by the patient (3). The most common adverse effects with primary vaginal dilation are bleeding, pain and urinary symptoms. Increasing use of lubricants and discontinuing treatment until bleeding ceases are the most commonly used approaches in the management of these complications (5).

In our case, an 18 year-old patient with CAIS, who wanted to engage in sexual activity, was referred to the gynecology clinic for the management of vaginal hypoplasia. Anatomical success with a 6 cm long vagina was achieved in two months and no complications or adverse effects were encountered. During the treatment, methods to decrease sexually transmitted infections, including the use of condoms were also reviewed and HPV vaccine was recommended, since patients with MRKH syndrome and CAIS are at risk of vulvovaginal HPV infection (10).

For patients with poor adherence or failure to succeed with dilation therapy or for those who do not wish to start vaginal dilation therapy, many surgical vaginoplasty methods have been described, including the Vecchietti procedure, McIndoe procedure and sigmoid vaginoplasty. In the literature, there is no consensus on the surgical technique to be chosen to achieve the best functional outcome and sexual satisfaction (11). Complications of these operations include injuries of adjacent organs, such as bladder or rectum, graft necrosis, neovaginal granulation tissue and fistulae. In the long term, all surgical methods carry a risk for vaginal stenosis or strictures, and long-term reoperation rates might be as high as 40% (1,12). Therefore, most procedures also require ongoing postoperative dilation to decrease the risk of stenosis.

Ethics

Peer-review: Internally peer-reviewed.

Informed Consent: Consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices: Şükran Poyrazoğlu, Concept: Şükran Poyrazoğlu, Design: Şükran Poyrazoğlu, Data Collection or Processing: Özlem Dural, Analysis or Interpretation: Özlem Dural, Literature Search: Özlem Dural, Writing: Özlem Dural.

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