ACTA SCIENTIFIC PAEDIATRICS (ISSN: 2581-883X)

Volume 2 Issue 12 December 2019

Comprehension Review

Primary Amenorrhea Evaluation and Management

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Received: November 05, 2019; **Published:** November 13, 2019

DOI: 10.31080/ASPE.2019.02.0182

Introduction

For normal menstrual cycles, there should be an intact hypothalamic pituitary, gonadal, and Mullerian systems. Gonadotropins act on the ovaries leading to secretion of estrogens and progesterone that act on the endometrium preparing it for implantation of the embryo. If no pregnancy, then the estrogen and progesterone will decline due to demise of the corpus luteum in the ovary, and menses starts [1,2].

The secondary sexual characteristics develop by age 13 in the form of breast and axillary and pubic hair. At this age also menses starts. If secondary sexual characteristics are not developed by age 13, then evaluation should be done to find the etiology and institute the treatment. Failure of menses to occur by age 15 years, in the presence of secondary sexual characteristics, the evaluation should be started [3].

Hypothalamic pituitary dysfunction

This results from decrease in the gonadotropin releasing hormone (GnRH) secretions from hypothalamus. This may be due to congenital absence of cells secreting this factor from the hypothalamus, a condition known as Kellman Syndrome [4]. Clinically these patients have hyposmia or anosmia due to failure of development of the olfactory bulb that is originating from the same cells that secrete GnRH. These patients are treated with cyclic estrogen and progesterone to develop the secondary sexual characters and menses.

Another factor that leads to hypothalamic pituitary dysfunction is amenorrhea due to anorexia and bulimia syndrome. This is a hypothalamic issue leading to decrease in GnRH and consequently to gonadotropins thus leading to amenorrhea. The management here is proper counseling [5].

Hypothalamic pituitary dysfunction also can result from heavy exercise activity like jogging and running long distances [6,7]. In all these cases, a thorough endocrine work up is completed to be sure there are no endocrine abnormalities leading to this syndrome including thyroid hormone abnormalities and hyperprolactinemia. Also MRI for the pituitary is to be completed to rule out a pituitary tumor.

Hyperprolactinemia can be idiopathic, or related to stress, exercise, or may be the result of a pituitary tumor known as prolactinoma. Elevated prolactin level leads to Hypogonadotropic Amenorrhea.

MRI of the pituitary is essential to reach the diagnosis. Treatment of this condition is medical using Bromocriptine that has been shown to decrease prolactin level and reduction of the size of the tumor [8].

Hyperprolactinemia may result from primary hypothyroidism. For the treatment of this condition, the use of thyroid replacement will normalize the prolactin levels, and thyroid levels, and leads to normal menstrual cycles [9,10].

Gonodal dysgenesis

There are several varieties leading to hypogonadism and amenorrhea.

Turner syndrome

These patients have one X chromosome. Karyotyping will show 45X as a result, the ovaries have no oocytes and they are streak

gonads. This will lead to primary amenorrhea, failure of breast development, and short stature, below 5 feet [11,12].

Pure gonadal dysgenesis

These patients show karyotyping of 46XX with streak gonads. They have normal height, absence of breast development, and primary amenorrhea. Another type is 46XY with streak gonads and absence of secretion of Mullerian inhibitory factor. They have Mullerian system, normal female external genitalia and normal height. There is no breast development. The treatment in these cases is gonadectomy and hormone replacement in the form of cyclic estrogen and progesterone [13]. Pregnancy has been reported by donated oocyte and Invitro fertilization [14].

Androgen insensitivity syndrome

These patients are XY females. They have failure of development of androgen receptors. At puberty, they have breast development, no axillary or pubic hair. The gonads are testicles. They secrete testosterone which is in the male level above 300 ng/dl. They also secrete a Mullerian inhibitory factor that inhibits the development of the Mullerian system. Therefore, they have no uterus or vagina. The treatment here is gonadectomy and estrogen-progesterone hormonal therapy. In addition, vaginoplasty is done to create a vagina either by using vaginal dilators or surgically using a skin graft [15,16].

Mullerian agenesis

The incidence of Mullerian agenesis is 1 in 4500 to 5000 females. These are 46XX females. At puberty they have normal breast development, and normal axillary and pubic hair [17]. Pelvic examination reveals absent vagina, and pelvic sonogram there is no uterus. There is failure of development of the Mullerian system. The ovaries are normal. The treatment is to develop a vagina by the use of dilators or if this is unsuccessful, then surgical vaginoplasty using skin graft could be done [18,19]. If pregnancy is the goal, the oocyte retrieval could be done and fertilization occurs invitro. The embryos will be implanted in a surrogate mother. This is also the same procedure followed in patients with androgen insensitivity syndrome with the use of donor egg program. In the near future, these patients will have also a uterine implant from a donor woman [20].

Imperforate hymen

The incidence of this anomaly is 1 in 1,000 newborn girls. It is usually diagnosed at puberty. The patient usually has normal adrenarche and pubarche and presenting with cyclic suprapubic pain without any menstrual flow. Inspection of the vulva shows normal labia majora and minora. The hymen is completely obstructing the introitus and bulging with menstrual blood distending the vagina. The treatment of such condition is surgical under anesthesia. A cruciate incision is done in the bulging hymen [21].

Transverse vaginal septum

This results from failure of canalization of the vaginal plate. The vaginal plate results from proliferation of cells at the junction of the Mullerian tubercle and urogenital sinus. The septum may be present in the upper middle or lower third of the vagina. If the septum is complete, then with the start of menstrual cycles, all the menstrual flow will collect above the level of the transverse vaginal septum. The patient will present with primary amenorrhea and cyclic lower abdominal pain. Sonography will show the Hematocolpos. The plan is surgical excision of the septum. The patient will then use vaginal dilators for 3-6 months [22].

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