***Amenorrhea***

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***Goal of this lecture: to make student able to approach patient with primary amenorrhea***

***Amenorrhea:*** *defined as the absence of menses*

***Clinical types:***

1. ***Physiological:***
* *Primary: Before puberty*
* *Secondary: During pregnancy, lactation, menopause*
1. *Pathological*
* *primary*
* *secondary*

***Primary amenorrhea****: when girls fail to menstruate by 16 years of age. Irrespective of the presence or absence of secondary sexual characteristics (the girl has never menstruated before)*

***Secondary amenorrhoea:*** *is absence of menstruation for more than 6 months in a normal female of reproductive age who had menses previously and that is not due to pregnancy, lactation or the menopause.*

***There are at least five basic factors involved in the onset and continuation of normal menstruation.***

1. *Normal female chromosomal pattern (46XX).*
2. *Coordinated hypothalamopituitary ovarian axis.*
3. *Anatomical presence and patency of the outflow tract.*
4. *Responsive endometrium.*
5. *Active support of thyroid and adrenal glands.*

***Primary amenorrhea***

***Etiology****:*

***I. Absent breast development; uterus present***

* 1. ***Gonadal failure:***
1. *45,X (Turner syndrome)*
2. *46,X, abnormal X (e.g., short- or long-arm deletion)*
3. *Mosaicism (e.g., X/XX, X/XX,XXX)*
4. *46,XX or 46,XY pure gonadal dysgene*
5. *17α-hydroxylase deficiency with* ***46,XX,*** *CAH*
	1. ***Hypothalamic failure secondary to inadequate GnRH release***
6. *Insufficient GnRH secretion because of neurotransmitter defect*
7. *Congenital ( Isolated gonadotrophin-relesasing hormone deficiency- Kallmann’s syndrome)*
8. *Congenital anatomic defect in central nervous system*
9. *CNS neoplasm (craniopharyngioma)*
	1. ***Pituitary failure***
10. *Isolated gonadotrophin insufficiency (thalassemia major, retinitis pigmentosa)*
11. *Pituitary neoplasia (adenoma)*
12. *Mumps, encephalitis*
13. *Newborn kernicterus*
14. *Prepubertal hypothyroidism*

*II. Breast development; uterus absent*

1. *Androgen insensitivity syndrome (Testicular feminization syndrome), 46 XY*
2. *Congenital Absence of the Uterus (Uterovaginal Agenesis, Mayer-Rokitansky-Küster-Hauser Syndrome)*

*III. Absent breast development; uterus absent*

1. *17, 20 desmolase deficiency*
2. *17 hydroxylase deficiency with* ***46,XY*** *karyotype*
3. *Agonadism*

***IV. Breast development; uterus present***

1. ***Hypothalamic cause:***
2. ***Psychological shock, stress, Anorexia nervosa***
3. ***strenuous exercise***
4. ***congenital malformation***
5. ***Trauma : Accidents, surgery or radiotherapy***
6. ***Infection : Tubercular or sarcoid granulomas***
7. ***CNS Tumors : e.g. craniopharyngioma, meningioma***
8. ***Pituitary cause:***
* ***Adenoma (eg.Prolactinoma)***
* ***Cushing’s disease***
* ***Acromegaly***
1. ***Ovarian cause:***
* ***Premature ovarian failure***
* ***Resistant ovarian syndrome***
* ***pelvic radiation***
* ***ovarian tumer: eg.Granulosa cell tumor,Sertoli-leydig cell tumor)***
1. ***Developmental defect of genital tract***
* *Imperforate hymen.*
* *Transverse vaginal septum*
1. ***Uterine cause:***
* ***Tubercular endometritis***
* ***Uterine synechiae (tubercular).***
* ***Postradiation***
* ***Surgical remove of uterus***
* ***Congenital absent of endometrium: genetic defect is responsible for this rare finding***
1. ***constitutional delay and secondary sexual characteristics are complete***
2. ***endocrine***
* *Juvenile diabetes.*

***Management***

*Investigation is started if*

1. *No periods by 16 years but secondary sexual characters are present.*
2. *No periods by 14 years in the absence of secondary sexual characters.*

***History***

1. *Aske other* ***stages of puberty****: Growth spurt, axillary and pubic hair, breast development(Lack of pubertal development suggests an ovarian/pituitary failure or a chromosomal abnormality)*
2. ***cyclical abdominal pain*** *and sometimes urinary retention suggestive of outflow obstruction*
3. ***Clinical features of virilization*** *eg.* ***Acne, hirsutism*** *(excessive growth of hair in normal and abnormal sites in female),* ***change in voice***
4. ***Recent changes in weight****( loss or gain) within short period of time*
5. *exercise habits, or recent life events causing stress*
6. ***History of visual field defects***
7. ***History of anosmia***
8. ***Past medical diseases*** *and ask about any chronic illness: eg. Cushing syndrome, tuberculosis or diabetes ,,Any neonatal and childhood diseases( eg.Neonatal crisis, suggestive of adrenal cause)*
9. ***sexual history***
10. ***drug history****, e.g. use of metoclopramide, antipsychotics, previous radiotherapy and chemotherapy*
11. ***family history*** *of the same problem (of delayed menarche) in the family or absent puberty*

***Examination:***

1. *height, weight, BMI*
2. *Tanner staging of breast and pubic hair development to assess pubertal development, galactorrhea, or androgen excess*
3. *feature of endocrine diseases( Hirsutism, acne, striae, increased pigmentation*
4. *Vitiligo—may be seen associated with autoimmune conditions of ovarian failure*
5. *Palpate thyroid gland*
6. *Stigmata of chromosomal abnormalities eg.Features of Turner’s syndrome—low hairline, webbed neck, widely spaced nipples.*
7. *Abdominal examination for masses*
8. *Genital examination:*
* *pubertal hair development*
* *Clitoral size(clitoromegaly)*
* *inspect the vulva for any abnormality such as*

*1- Tense bulging bluish membrane (imperforated hymen)*

*2-vaginal septum*

* *rectal examination :for the Presence of cervix and uterus*
1. *Assess visual fields and CNS examination (Kallmann syndrome or pituitary tumor)*

***Investigation***

1. *The first step in the work-up of primary and secondary amenorrhea is a pregnancy test*
2. ***Bone X-ray’s*** *for age estimation.*
3. ***Pelvic ultrasound*** *- Rarely may need* ***MRI or CT of the abdomen scanning*** *to assess pelvic anatomy.*
* *for presence or absence of the uterus and ovaries*
* *to detect hematocolpos and hematometra*
1. ***karyotype******:***
* ***46XY*** *:* *Andogen Insensitivity (TSF syndrome)*
* ***45X0 –turner syndrome***
1. ***LH, FSH:***
* ***Elevated LH, FSH:*** *Hypergonadotropic Hypogonadism ( eg.gonadal dysgenesis)*
* ***Low LH, FSH****: Hypogonadotropic hypogonadism (intracranial leasion)*
1. ***Prolactin levels****:Elevated**indicates* ***Prolactinoma***
2. ***X-ray or CT or MRI imaging******of pituitary fossa*** *: to rule pituitary tumors*
3. ***Thyroid function test(T3,T4,TSH)***
4. ***GnRH stimulation test:*** *If GnRH administered*
* *increase pituitary gonadotropins( LH ,FSH) is the probable cause is hypothalamic dysfunction*
* *no rise of gonadotropins( LH, FSH): pituitary disorders*
1. ***serum progesteron:***
* *high serum progesteron: sent for 17-OH-progesterone, Urinary pregnanetriol and cortisol*
* *Low in : Resistant ovary syndrome ,Gonadal agenesis*
1. ***Ovarian biopsy*** *if suspect Resistant ovary syndrome****. Histopathology*** *illustrating absence of oocytes.*

*Treatment*

***Is based on the etiology***

1. ***If constitutional delay and secondary sexual characteristics are complete*** *no need to suggest any treatment apart from annual review until she has menstruation, some use COC pills to promote menstruation as this will reassure her that menstruation can occur..*
2. ***Outflow obstruction:*** *Surgical management*
3. *Imperforate hymen; cruciate incision of the hymen or hymenectomy.*
4. *Transverse Vaginal Septum; Excision of the septum depending on its level within the vagina.*
5. ***Absent uterus:***
* *Girl managed by special psychological counseling as she got problem regarding their future sexual activity & infertility.*
* *Vagina is created at appropriate time (Vaginoplasty ) by surgical or non- surgical way using vaginal dilators.*
* *Girl with XY Karyotype: The gonads should be removed after puberty( Gonadectomy ). because of increased development of seminoma or dysgerminoma*
1. ***Unresponsive endometrium(rare)***

***– For TB synechiae: Adhesiolysis followed by insretion of IUCD and high dose of estrogen and progesterone to prevent recurrent and for withdrawal bleeding***

***– Receptor abnormal (very rare)—no treatment***

1. ***Turner’s syndrome****:short-term use of estrogen and progesterone at least for the development of secondary sex characters*
2. ***Hypothalamic-pituitary ovarian axis defect***
* *Severe defect may not respond*
* *isolated gonadotropin deficiency (like Kallmann’s syndrome) responds to pulsatile GnRH (for ovulation) and estrogen, progesterone (for menstruation)*
* *Hypothalamic-pituitary tumors eg.(craniopharyngioma) may need surgical excision or radiotherapy*
* ***If pituitary microadenoma:*** *then treatment is with Bromocriptine or Cabergoline, macroadenoma may necessitate surgery or radiotherapy*
1. ***Thyroid and adrenal diseases:***
	* ***(Cretinism)*** *do not respond to thyroxin. Mild hypothyroids respond well*
	* ***Adrenogenital syndrome*** *with enlarged clitoris treated by excise clitoris (clitoroplasty) as early as possible to avoid psychological trauma*
	* ***Corticosteroids*** *are useful in17 α hydroxylase deficiency*
2. ***Metabolic and nutritional diseases:***
	1. *Hypoglycemic agents and insulin in case of* ***diabetics***
	2. *Anti-TB treatment for* ***TB***
	3. ***Anemia*** *treatment*
	4. ***Malabsorption*** *to be treated*
	5. *Adequate nutrition in case of weight loss*

***TURNER’S SYNDROME (45X AND MOSAICS)***

* *Is the most common karyotypic abnormality causing gonadal failure (nonfunctional streak ovaries) and primary amenorrhea.*
* *Mosaicism (45,X/46,XX) may occur; these women may have some ovarian function through early adulthood, and may become pregnant, but then progress to secondary amenorrhea*
* ***it is characterized :***
1. ***At birth by:***
* *low weight*
* *short stature*
* *edema of the hands and feet*
* *Loose skin folds on the neck.*
1. ***Adolescent patients have :***
2. *short stature;*
3. *ovarian failure: no secondary sexual development in most cases, primary amenorrhea*
4. *occasionally secondary amenorrhoea in mosaicism;*
5. *low hair line.*
6. *webbed neck*
7. *Shield chest with widespread nipples*
8. *Scoliosis*
9. *epicanthal folds*
10. *renal dysgenesis*
11. *Horseshoe kidney*
12. *left-sided cardiac malformations, coarctation of the aorta;*
13. *distortion of the Eustachian tube leading to otitis media;*
14. *nail dysplasia*
15. *increased carrying angle at the elbow(cubitus valgus)*
16. *short fourth metacarpal;*
17. *high, arched palate, micrognathia and defective dental development;*
18. *Streak gonads: do not need to be removed as there is no Y chromosome present and no risk of malignancy.*
19. *Intelligence is usually normal, but there is risk of impairment of non-verbal skills, e.g. maths*



***3. There are a number of long-term health medical problems:***

1. *hypertension; coarctation of the aorta; bicuspid aortic valve; dissecting aortic aneurysm; diabetes; hypothyroidism; coeliac disease;*
2. *sensorineural hearing loss; renal disease; eye problems – red–green colour blindness and increased risk of osteoporosis.*
3. *Premature mortality in women with Turner’s syndrome is 3 times higher than in the general population.*
4. *After treatment with donor oocytes. Clinical pregnancy rates are reported to be comparable to those of other women with primary ovarian failure but there is an increased risk of com­plications including diabetes and hypertension in the preg­nancy, and delivery by caesarian section (CS) may be required because of the woman’s short stature.*

***Treatment:***

*A low dose of estrogen is given initially to encourage steady growth of the breasts; this is usually started after the age of 12 years as the administration of estrogen promotes epiphyseal fusion, which stops further growth. The dose of estrogen is gradu­ally increased over 2 years.*

 *The uterus will respond to estrogen therapy, so after 2 years it is necessary to add progestogens cyclically to produce regular endometrial shedding, or in a continuous combined regime to suppress endometrial development. HRT should be continued until at least the age of 50 years. For girls with mosaicism. Cryopreservation of ovarian tissue may be an option for future fertility.*

*Thank you*