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During week 6 of fetal life, the primitive gonads appear on the urogenital ridge, medial to the mesonephros, and the mesonephric (Wolffian) and paramesonephric (Müllerian) ducts develop. It has been suggested that Wolffian ducts act as a precursor/inducer for Müllerian formation or as a guide in the downward growth of the Müllerian ducts . By the seventh week, the *SRY* gene (the sex-determining region of the Y-chromosome) in male embryos stimulates gonadal differentiation into testes; these produce androgens and anti-Müllerian hormone, which promote the development of male internal genitalia from the Wolffian ducts, cause regression of Müllerian structures and cause virilization of the indifferent external genitalia. Conversely, absence of the *SRY* gene in female embryos allows the gonads to develop into ovaries. The subsequent lack of anti-Müllerian hormone causes regression of the Wolffian ducts and allows Müllerian ducts to develop into fallopian tubes, the uterus and upper vagina, while the lack of androgens permits differentiation of the indifferent external genitalia into the labia majora, labia minora and the clitoris. Müllerian development occurs separately from gonadal development, and women with Müllerian anomalies usually have normal ovaries and ovarian hormone production . By contrast, Müllerian development occurs in close association with the development of the urinary tract, and renal anomalies are commonly identified in those with Müllerian anomalies

Primary Amenorrhea

3%

Definition

. Absence of menstruation(never seen menstrual cycle)

. Investigated at age of 14 years if there are no 2ry sexual characteristics or age of 16 with 2ry sexual char.

Pathophysiology- classifcation

.Anovulation

.Ovarian

.Pituitary

.Hypothalamic

.Amenorrhea secondary to systematic disease

. Anatomical… uterine & outflow obstruction

Clinical evaluation

.History

- chronic systemic illness such as D.M, cystic fibrosis, R.F
- History of delayed puberty in mother or sibling
- Anosmia (suggestive of Kallman's)
- Excessive exercise or competitive sports
- Anorexia nervosa
- Childhood cancer requiring chemotherapy or radiotherapy
- Cyclical pelvic pain.

. Examination

- Stature - BMI - Breast development

-Presence of pubic and axillary hair - Inguinal masses - Hirsutism and evidence of virilism

Investigations

- *FSH and LH*
- *Oestradiol level*
- *Peripheral blood karyotype*
- *Pelvic imaging studies (U/S and MRI)*
- *Approach:*

.The presence or absence of 2ry sexual ch. Along with gonadotropins(FSSH,LH) levels help make an initial assessment of the possible causes of amenorrhea. Normal breast development usually indicates that there is normal ovarian function, or that there has been at some point.

. *Low gonadotropins → Dysfunction of the hypothalamus or pituitary*

. *High gonadotropin → Failing gonads*

. *Normal level → Suggest anatomical defect*

Cont.

. *A girl with primary amenorrhea falls into one of four followings:*

1- Absent breast development and low FSH

Central defect or constitutional(family history)

2- Absent breast development and high FSH

The defect lies in the gonad which has no hormonal or reproductive potential

A karyotype is required to differentiate :

- Turner syndrome(45 XO)

- POF (46 XX)

- Swyer syndrome (46XY)

..... She has a uterus that can be missed (small prepubertal size)

Cont.

3- Normal breast development and high FSH

.....Puberty is arrested, karyotype and pelvic imaging study to differentiate:

- POF (46XX), uterus present

- Complete androgen insensitivity (CAIS), 46XY, uterus absent, absence pubic and axillary hair which are androgen dependent and short vagina.

4- Normal breast development and Normal FSH

..... Anatomical defect, pelvic imaging study to classify into:

- Absent uterus (Mayer- Rokitansky-Kuster-Hauser syndrome)

- Obstructive anomalies(imperforated hymen, vaginal septum, vaginal agenesis and cervical agenesis)

Management

The management depend on the cause:

- Hormonal replacement may be required for induction of puberty and to protect against from osteoporosis in long term

- Intervention may be required to expand the vagina to allow sexual intercourse(CAIS and MRKH)

- Fertility and sexual implications....Psychological support.

- Fertility can be achieved by assisted conception..... Ovum donation

Secondary Amenorrhea

.**Secondary amenorrhea:** is the absence of menstrual periods for 6 months in a woman who had previously been regular, or for 12 months in a woman who had irregular periods

.This problem is seen in about 1% of women of reproductive age.

.Secondary Amenorrhea is a Symptom

Secondary amenorrhea is a symptom that can be caused by many pathological states. The diagnostic evaluation should lead to the correct diagnosis if the problem is approached in a logical stepwise manner

1 - Patient History

A good history can reveal the etiologic diagnosis in up to 85% of cases of amenorrhea.

A detailed menstrual history should be taken.

Cont.

2 - Physical Examination

Signs of androgen excess such as hirsutism (excess hair growth) and clitoromegaly (enlargement of the clitoris).

The breast exam may reveal galactorrhea (milky discharge from the breasts).

Estrogen deficiency may be suggested on pelvic exam by a smooth vagina that lacks the normal rugae (wrinkles) and a dry endocervix with no mucous.

3 - Suggest Certain Etiologies from History and Exam

If the history and physical exam are suggestive of a certain etiology then the initial workup can be tailored appropriately.

Cont.

4 - Perform Diagnostic Evaluations

Some patients will not demonstrate any obvious etiology for their amenorrhea on history and physical exam. These patients can be worked up in a logical manner using a stepwise approach.

Diagnostic approaches may vary, however, differences pertain mainly to the order in which tests are performed.

There are several ways that a workup for secondary amenorrhea can be approached. One reasonable diagnostic approach is described here. If your doctor did things differently, that doesn't mean that he or she was wrong or that this approach is wrong. Every case should be treated individually.

Cont.

Diagnostic Evaluation

1.**TFT**: Both hyperthyroidism and hyperprolactinaemia can cause primary or secondary amenorrhea. If present, medication therapy should result in return of regular periods.

2. **The progestational challenge test** is performed by giving a progestin (medication).

If the patient experiences withdrawal bleeding after the progestin medication is stopped then she has estrogen present but is not ovulating (anovulation).

If no withdrawal bleeding occurs, either the patient has very low estrogen levels - or there is a problem with the outflow tract such as uterine synechiae (adhesions) or cervical stenosis (scarring).

Cont.

Possible Diagnoses for Women with Withdrawal Bleeding

Anovulation

Polycystic Ovarian Disease (PCOS)

-Chronic anovulation should be managed by periodic progestin withdrawal, or oral contraceptive pills if the patient does not currently desire pregnancy.

If she desires pregnancy, induction of ovulation with clomiphene citrate or injectable gonadotropins can be considered.

If the anovulatory state has been longstanding, endometrial biopsy should be considered to rule out significant hyperplasia or carcinoma of the endometrium.

Cont.

Possible Diagnoses for Women without Withdrawal Bleeding

Hypoestrogenism - low estrogen levels

Compromised outflow tract - either Asherman's syndrome (adhesions) or cervical stenosis (scarring)

Premature ovarian failure (POF or POI, or "early menopause")

If adhesions are found, they should be hysteroscopically lysed if the woman wants pregnancy or regular periods.

3 - FSH testing

If the patient did bleed after the combined hormonal regimen (or if that step was skipped) the next test to obtain is an FSH level. This should not be drawn for about 2 weeks after the estrogen-progestin regimen is completed so that the hormone levels are not affected by the medications.

FSH Levels Indicating Ovarian Failure

If the FSH is greater than 30-40 MIU/ml, the patient probably has ovarian failure.

Midcycle FSH peak levels in ovulatory cycles should not be this high.

FSH levels that are menopausal should be checked again in a few weeks for confirmation

An estradiol level can also be done. With ovarian failure, estrogen is low (less than 20-40 pg/ml).

Cont.

Ovarian Failure (Premature Menopause)

Once ovarian failure is confirmed, consideration should be given to 3 possibilities:

-Mosaicism involving a X chromosome

-Fragile X syndrome

-Autoimmune disease

Cont.

Hypothalamic Amenorrhea

Patients who do not bleed after the progestin challenge but do bleed after estrogen/progestin and have normal or low FSH and LH levels have hypothalamic amenorrhea.

Hypothalamic dysfunction results in abnormal release of LH and FSH hormones from the pituitary. The end result is a lack of proper follicle development and ovulation.

Possible Causes of Hypothalamic Amenorrhea

Some medications (e.g. phenothiazines) as well as extremes of weight loss, stress or exercise can cause this type of secondary amenorrhea.

A pituitary or hypothalamic tumor would be a rare finding in these patients who were all screened with prolactin levels at the beginning of the diagnostic evaluation. However, if there is no cause apparent from the history, it is sometimes suggested to get a baseline CT or MRI scan of the sellar region to rule out a (very rare) tumor.

Treatment

hypothalamic amenorrhea situations, the patients can be significantly hypoestrogenic (a low estrogen situation similar to menopause).

Treatments

If the state is persistent, hormone replacement therapy should be considered for protection against osteoporosis.

One approach is to get an estradiol level and if it is less than 30 pg/ml, counsel the patient that hormonal replacement therapy is indicated.