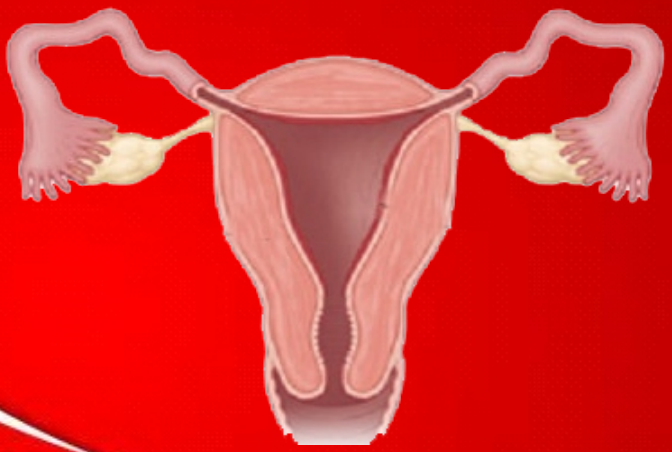
FOGSI FOCUS 2021

AMENORRHOEA



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Dr. S. Shantha Kumari
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Dear FOGSIANS

It is indeed a formidable and challenging task to don the mantle of the President of FOGSI and step into the shoes of the stalwarts and doyens who have brought laurels to FOGSI during their tenure as President. But my confidence is boosted and gets a fillip since I will be supported by my new team of office bearers each of whom have rightfully earned their place in our organisation.

I would like to congratulate Dr Anita Singh Vice President FOGSI East Zone and her team of contributors to FOGSI Focus dedicated to the common and often perplexing clinical problem of amenorrhea. This issue covers the topic of amenorrhea from various perspectives to give a holistic view off this distressing entity. Its management often oversteps the confines of a gynecologist's domain to ask for solutions from endocrinologists and imaging specialists in the quest to ascertain the diagnosis and decide upon a satisfactory management protocol for the patient ideally individualized for every patient.

Seasoned old time consultants and fresh- in- the -field budding gynaecologists will fall back on it with relief when hard pressed for time coupled with the urgency to manage girls and women with amenorrhea in their daily clinical practice.

Happy reading and reflecting on past experiences of our own encounters with amenorrhea.

FOREWORD

Dear FOGSIANS, 12th June, 2021

It gives me immense pleasure to write this foreword for the FOGSI FOCUS on 'Amenorrhea' which is being edited by our dear and hardworking Dr. Anita Singh, Vice President FOGSI, 2020 .The entire team of Vice Presidents and chairpersons working with Dr. Alpesh Gandhi as President FOGSI, 2020 has done very commendable work, for FOGSI socially, academically and for the fraternity.

The **prevalence** of **amenorrhea** is approximately 3,000 to 4,000 per 100,000 individuals worldwide. Amenorrhea can be a very perplexing problem if not attended to in an appropriate manner.

The treatment for amenorrhea depends on the underlying cause. So taking a detailed history, counselling and reassurance of the girl and her parents is a very essential part of the management . If primary or secondary amenorrhea is caused by lifestyle factors, destressing, change of weight and physical activity may help . But if there are constitutional factors, congenital factors, endocrinological issues, it needs a multidisciplinary approach and one must do this at the appropriate time and systematic manner.

This FOGSI FOCUS covers all aspects of amenorrhea starting from diagnosis to treatment . Understanding basic examination and screening tests would enable gynecologists to diagnose and treat women.

Hearty Congratulations to Dr. Anita Singh and her team of authors who have contributed to this FOGSI FOCUS. We are sure this will be a ready reckoner for clinicians and facilitate in their diagnosis and management of Amenorrhea.

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PREFACE

In continuation with its well-established tradition, FOGSI Focus continues its publication journey devoted to clinical problems encountered by gynecologists and obstetricians in their patient encounters. Amenorrhea is one such front-line problem with far-reaching and over-arching implications on a woman's health.

In this issue we have compiled inputs of eminent, seasoned clinicians who provide clinical insights into the problems of amenorrhea from various perspectives. The chapters are listed on the basis of their etiology. Each chapter elaborates on the etio-pathogenesis followed by the clinical presentation and management options available, and which need to be discussed during patient counseling.

This crisp but comprehensive capsule of information between the covers of this issue of FOGSI Focus will come in handy and useful to consultants and post-graduate students alike as they confront a girl or woman who is worried about the absence or cessation of her menstrual periods.

We are grateful to our President Dr Alpesh Gandhi who entrusted this academic task to us and extend our sincere thanks to the contributors in this issue who found time from their busy schedule to send in their write-ups.

Dr. Alpesh Gandhi

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Dr Tripti Sinha

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Amenorrhea: An Overview

Dr Anita Singh

Dr Tripti Sinha

Menstruation is of great significance and concern to any woman and her healthcare-provider. The cessation of menstruation is of even greater concern to both and naturally sparks the question: why did menstruation stop? What are the implications of its cessation in the short and long term? The answers would be contextual and need to be individualized.

Physiological Basis of Menstruation

In order to understand the etio-pathogenesis of amenorrhea it is imperative to look into the physiological basis of menstruation. Although the outward manifestation of menstruation is the outflow of menstrual blood through the vaginal orifice, it is only the end-stage of a complex chain of events starting at the higher centers in the hypothalamus linked to the events at successively lower levels in the pituitary and ovary with some confounding controls by other endocrine glands notably the thyroid and adrenals. It is, therefore, not difficult to understand why investigating a case of amenorrhea involves methods and assays which look into the normalcy or otherwise of the entire HPO –axis as well as the reproductive outflow tract. Figures 1 and 2 are simplified schematic and pictorial representations of the events leading to menstruation and the controls at various levels.

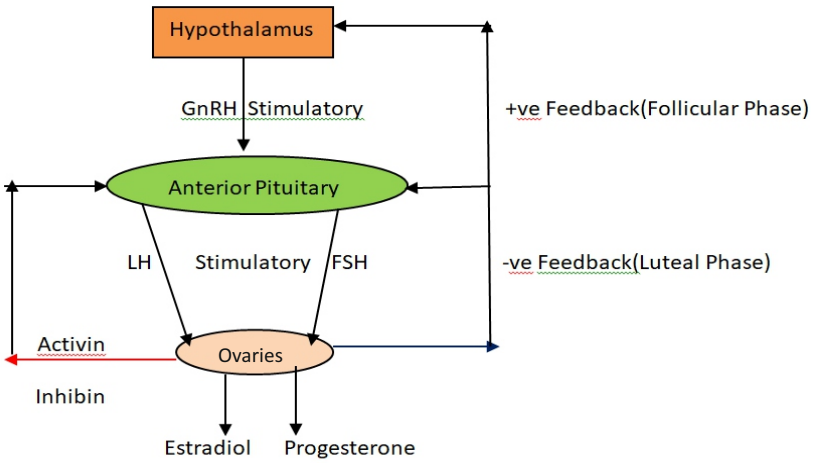


Figure 1: Simplified schematic representation of the events leading to menstruation and controls at various levels

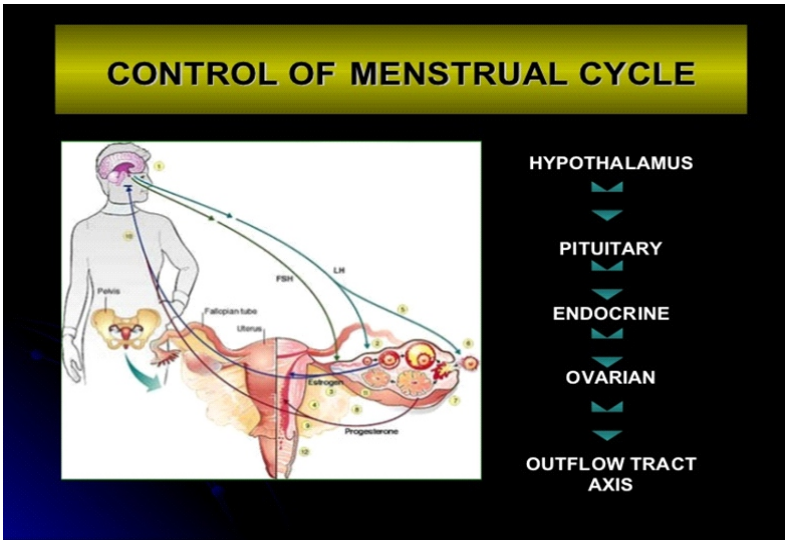


Figure 2: The hypothalamic-pituitary ovarian axis integrated to the reproductive outflow tract

The menstrual cycle is divided into the following cyclical and sequential phases: menstruation, early and late follicular/proliferative phase, ovulation, early and late luteal/secretory phase followed by its repetition at regular or irregular cycle lengths which may vary in women and often in the same woman at different periods in her reproductive age span. The different phases of each menstrual cycle have their own hormonal milieu and endometrial histology.

The levels of progesterone, estradiol and inhibin-A from a waning corpus luteum dip pre-menstrually triggering a positive feedback on the anterior pituitary to release more follicle-stimulating hormone (FSH) to recruit ovarian graffian follicles with its oocytes for the next cycle. Gonadotropin –releasing hormone(GnRH) of hypothalamus is released into the intra-cranial portal circulation in the vicinity of the pituitary gland in a pulsatile manner to initiate the follicular phase. The estradiol and inhibin-B from the developing graffian follicles provide negative feedback to pituitary FSH secretion so that it wanes by mid-follicular phase. Pituitary luteinizing hormone(LH) follows a reverse profile in follicular phase, decreasing initially with rising estradiol of early follicular phase but later rising drastically late in follicular phase(biphasic response). Just before ovulation, FSH-induced LH receptors are produced on granulose cells which subsequently with LH stimulation modulate progesterone secretion. After adequate estrogen the pituitary LH surge is triggered leading to ovulation 24-36 hours later. In the subsequent early luteal phase till mid-luteal days the estrogen decreases and again rises as a secretion from the corpus lureum. Inhibin –A is also secreted concomitantly by the corpus luteum stimulation. Dramatic progesterone rise in this period of the menstrual cycle is a surrogate marker for previous ovulation occurrence. Progesterone, estrogen and inhibin –A act in tandem on the central hypothalamic-pituitary axis in the luteal phase and effectively suppress gonadotropin secretion and new follicular growth. As the corpus luteum withers and dies these hormones decline thus preparing for the subsequent cycles in an orderly sequence. A more elaborate description of the menstrual physiology is beyond the scope of this introductory chapter on amenorrhea. (1)

Health implications depend to a large extent on the etiology of amenorrhea. Hence, the need to establish the cause of amenorrhea over-rides all other concerns while planning its management. The HPO axis must be normal anatomically and function synchronously at various levels in order that neuro-transmitters and hormones exert a normal end-organ effect on the endometrium ensuring its cyclical shedding off at the time of menstruation.

This opening chapter of FOGSI Focus dedicated to the problem of amenorrhea gives a brief capsular overview of the subject and sequentially clarifies basic concepts related to amenorrhea so that the subsequent chapters are seen in their proper perspective. Amenorrhea is discussed under the following headings:

- Definition
- Classification/types of amenorrhea
- Epidemiology
- Causes of amenorrhea and their classification
- Implications of amenorrhea: short term and long term
- Management issues including patient counseling

Definition :

As a simple definition, amenorrhea is the absence or cessation of menstruation. An adolescent girl or woman in the reproductive age group who has never had spontaneous menstruation has primary amenorrhea while a woman who was previously menstruating cyclically/acyclically but has currently ceased to do so has secondary amenorrhea. The terms primary and secondary are further elaborated upon in the next section on classification /types of amenorrhea.

From a care-givers point of view, patients fulfilling the following criteria merit evaluation for evaluation.

1. No menses by the age of 14 in the absence of growth/development of secondary sexual characteristics
2. No menses by the age of 16 regardless of the presence of normal growth/development of secondary sexual characteristics
3. In previously menstruating women , no menstruation for an interval of time equivalent to a total of at least three previous cycles or no menses over a 6 month period(2)

Classification/types of amenorrhea:

It helps in classifying the etiology of amenorrhea from different perspectives: its time of onset, the level at which the etiological factor operates and the presence and absence of secondary sexual characteristics. This clarity through classification helps the clinician to guide his workup for that particular patient. Management gets simplified if the above etiological causes are initially categorized as physiological or pathological on the basis of the patient's history. The pathological group is further categorized into primary and secondary amenorrhea. This then helps to target more definitively the level at which any defect operates.

Depending on the time of its onset, amenorrhea may be classified as primary and secondary amenorrhea.

A} Primary: a girl who has achieved the age of 14 years but has not menstruated nor shown visible signs of development of secondary sexual characters, or a girl who has reached 15-16 years of age with developed secondary sexual characters but not menstruated spontaneously are classified as having primary amenorrhea and merit investigation and appropriate management.

B} Secondary: a woman previously having menstruation has failed to menstruate for the last few months equivalent to her previous three menstrual cycles at least or for the past six months is considered to have secondary amenorrhea.

Primary Amenorrhea	**Secondary Amenorrhea**
Constituitional delay(14) %	Chronic anovulation(39%)
Gonadal failure/ dysgenesis (43%)	Hypothyroidism
Imperforate hymen	Hyperprolactinemia
Congenital absence of uterus and vagina	Extreme weight change (anorexia/bulimia)
Hypothalamic failure(Kallman's syndrome)	Cushing's syndrome
Androgen insensitivity (Testicular Feminisation syndrome)	Adrenal tumors
	Androgen producing ovarian tumors
	Premature ovarian insufficiency/ failure
	Pituitary infarction(Sheehan's syndrome)
	Surgical extirpation of uterus &/or ovaries
	Radiotherapy
	Chemotherapy

Table 1 Summarises the causes of primary and secondary amenorrhea.

Based on its etiology, amenorrhea is classified as follows:

A} Physiological: amenorrhea in pre-pubertal age group, following physiological natural menopause, during pregnancy and lactation. Physiological amenorrhea does not need any intervention apart from observation and documentation of future menstrual cycles and/or vaginal bleeding episodes.

B} Pathological: amenorrhea arising from any other cause apart from the above should induce the care giver to logically investigate its cause on the basis of and anatomical and physiological basis of menstruation and its likely aberrations in the index case. These causes may be congenital or acquired.

Causes of amenorrhea and their classification

There is an exhaustive list of pathological causes of amenorrhea. The causes have been logically classified in the WHO classification and by others working in the field of reproductive endocrinology .

In the WHO classification of amenorrhea originally there were only three groups; the fourth group was added subsequently.(3)

Group 1 Hypo-gonadotropic hypo-gonadism (27.8%),

Group 2 Normo-gonadotropic anovulation (23.7%)

Group 3 Hyper-gonadotropic hypo-gonadism (48.5%)

Group 4 Hyper-prolactinemic anovulation

Level of lesion	Type of lesions
Hypothalamic	Craniopharyngioma, Germinoma, Tubercular granuloma, sarcoid granuloma, dermoid cyst , Kallman syndrome
Pituitary	Craniopharyngioma, Germinoma , Tubercular granuloma, sarcoid granuloma, dermoid cyst, Non-functioning adenomas Hormone - secreting adenomas(prolactinoma, Cushing disease, acromegaly Infarction Lymphocytic hypophysitis Surgical/radiotherapy -induced ablations Sheehan syndrome Diabetic vasculitis
Ovary	Gonadal dysgenesis, FSH/LH hormone receptordefect, environmental & therapeutic ovarian toxins, galactosemia, Sex chromosome mosaicism, partial deletion of X chromosome, 17 -α hydroxylase deficiency in XX/XY individual ,ovo-testicular di sorder,
Uterus	Mayer-Rokitstansky - Kuster-Hauser syndrome, absent endometrium, Asherman syndrome(2*curettage, electro -excision, severe acute PID, tuberculosis, schistosomiasis
Vagina	Imperforate hymen, transverse vaginal septum
Miscellaneous	Androgen insensitivity

Table 2: Etiological causes of amenorrhea operating at different levels of the HPO axis and reproductive outflow tract

After clinical examination, each patient can be categorized into one of two groups on the basis of absence or presence of secondary sexual characteristics (Table 3).

Secondary Sexual Characteristics Absent	Secondary Sexual Characteristics present
Physiological delay	Mullerian agenesis (imperforate hymen, transverse vaginal septum, Mayer-Rokitstansky-Kuster-Hauser syndrome)
Gonadal dysgenesis	Androgen insensitivity
FSH/LH receptor defect	Ovo-testicular disorder
Sex chromosome mosaicism	Absent endometrium
Partial deletion of X chromosome	Asherman's syndrome
Kallman's syndrome	Severe intra- uterine infections(tuberculosis,PID, schistosomiasis
CNS Tumors	
Hypothalamic/pituitary dysfunction	
Enzyme deficiencies in XY individuals(5α–reductase, 17,20-lyase,17 α- reductase)	
Galactosemia	
Congenital lipoid adrenal hyperplasia	
Environmental & therapeutic ovarian toxins	

Table 3: Causes of amenorrhea with and without development of secondary sex characteristics

Emerging iatrogenic causes of amenorrhea include radiotherapy and chemotherapy for malignancies as well extirpative surgery on uterus and ovaries. An expanding list of medications frequently prescribed to women needs to be kept in mind thus emphasizing the importance of a rigorous medical and medication history.

Table 4 is a comprehensive list of etiological causes compiled by the the American Society of Reproductive Medicine.(4)

I. Anatomic defects (outflow tract) A. Mullerian agenesis (M -R-K-H syndrome) B. Complete androgen resistance (testicular feminization) C. Intrauterine synechiae (Asherman syndrome) D. Imperforate hymen E. T ransverse vaginal septum F. Cervical agenesis —isolated G. Cervical stenosis —iatrogenic H. Vaginal agenesis —isolated I. Endometrial hypoplasia or aplasia — congenital	**III. Hypothalamic causes** A. Dysfunctional 1. Stress 2. Exercise 3. Nutrition -related a. Weight loss, diet, malnutrition b. Eating disorders (anorexia nervosa, bulimia) 4. Pseudocyesis B. Other disorders 1. Isolated gonadotropin deficiency a. Kallmann syndrome b. Idiopathic hypogonadotropic hypogonadism 2. Infection a. Tuberculosis b. Syphilis c. Encephalitis/meningitis d. Sarcoidosis 3. Chronic debilitating disease 4. Tumors a. Craniopharyngioma b. Germinoma c. Hamartoma d. Langerhans cell histiocytosis e. Teratoma f. Endodermal sinus tumor g. Metastatic carcinoma
II. Primary hypogonadism A. Gonadal dysgenesis 1. Abnormal karyotype a. Turner syndrome 45,X b. Mosaicism 2. Normal karyotype a. Pure gonadal dysgenesis i. 46,XX ii. 46,XY (Swyer syndrome) B. Gonadal agenesis C. Enzymatic deficiency 1. 17a-Hydroxylase deficiency 2. 17,20-Lyase deficiency 3. Aromatase deficiency D. Premature ovarian failure 1. Idiopathic 2. Injury a. Chemotherapy b. Radiation c. Mumps oophoritis 3. Resistant ovary a. Idiopathic E. Ovarian tumors 1. Granulosa-theca cell tumors 2. Brenner tumors 3. Cystic teratomas 4. Mucinous/serous cystadenomas 5. Krukenberg tumors 6. Metastatic carcinoma	**IV. Pituitary causes** a. Tumors 1. Prolact inomas 2. Other hormone-secreting pituitary tumor (ACTH, thyrotropin-stimulating hormone, growth hormone, gonadotropin) b. Mutations of FSH receptor c. Mutations of LH receptor d. Fragile X syndrome B. Space-occupying lesions 1. Empty sella 2. Arterial aneurysm C. Necrosis 1. Sheehan syndrome 2. Panhypopituitarism D. Inflammatory/infiltrative 1. Sarcoidosis 2. Hemochromatosis 3. Lymphocytic hypophysitis E. Gonadotropin mutations (FSH)
V. Other endocrine gland disorders A. Adrenal disease 1. Adult-onset adrenal hyperplasia 2. Cushing syndrome B. Thyroid disease 1. Hypothyroidism 2. Hyperthyroidism	**VI. Multifactorial & other causes** 1. Polycystic ovary syndrome 2. Autoimmune disease 3. Galactosemia

Table 4: Classification of amenorrhea (not including disorders of congenital sexual ambiguity)-adapted from the American Society of Reproductive Medicine

Management issues including patient counseling

No consensus has been reached regarding the point at which oligomenorrhea becomes amenorrhea. Some authors suggest the absence of menses for 6 months constitutes amenorrhea, but the basis for this recommendation is unclear. For a post-menarchal girl or a reproductive-aged woman to experience a menstrual cycle interval of more than 90 days is statistically unusual. Practically speaking, this should be an indication for a thorough evaluation to seek the cause.

Important clinical considerations in management of amenorrhea involve the following issues:-

1) To manage actively or merely to keep under observation currently
2) Management modalities for active intervention
3) How long to continue the intervention

Amenorrhea warrants investigations if it occurs in periods of life when physiological amenorrhea does not occur. It is prudent clinical practice to consider all cases of amenorrhea in women of reproductive age group to be pregnant unless proved otherwise.

Management often involves inputs from other medical disciplines notably internist, endocrinologist, neuro-surgeon and psychiatrist. However, most cases can be managed by gynecologists and even primary healthcare physicians provided their management plan is derived from a clear concept of the HPO axis and the reproductive outflow tract anatomy.

Certain clinical points need to be kept in mind while investigating a case of amenorrhea. First, though the distinction between primary and secondary amenorrhea is important from the purpose of classification sometimes the cause may overlap both primary and secondary amenorrhea (Figure 3). Secondly, a girl showing obvious clinical stigmata of certain disorders like Turner's syndrome or vaginal agenesis may be evaluated earlier even before the normal age of menarche and puberty and the parents counseled regarding her management and prognosis holistically.

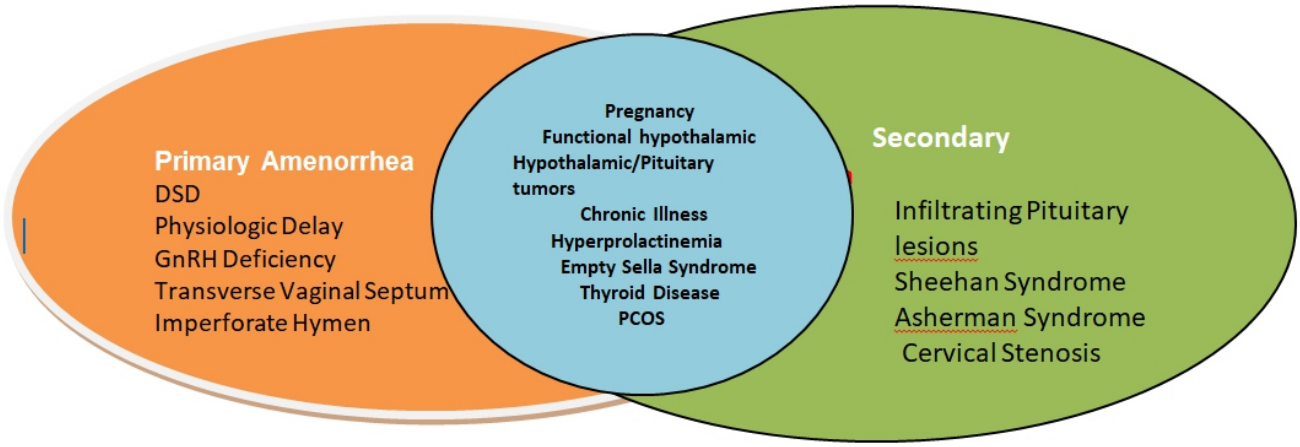


Figure 3: Discrete and overlapping causes of primary and secondary amenorrhea

A well taken history may reveal the correct etiology of amenorrhea in up to 85% cases. The initial consultation should be devoted to a systematic elaborate history-taking followed by a complete methodical physical examination of not only the gynecological organs per se but all systems in general since amenorrhea may be merely one of the worrying manifestations of a disease which secondarily involves the gynecological system of the woman.

History- taking commences with questions related to menstrual-type pains and/or menstrual molimina in a girl who does not report menarche. In such girls the time since when breast development commenced should be enquired into. Women who cease to have periods after a previously menstruating should be asked to elaborate on their previous menstrual details especially whether lengthening cycles or progressively reduced flow had culminated finally in the amenorrhea. In a young girl it is important to clarify whether she only had menstrual-type bleeds

following hormone intake prescribed elsewhere. Such a history categorises her as a case of primary amenorrhea rather than secondary amenorrhea who responded as a positive hormone challenge withdrawal bleed and gives a pointer to likely etiologies of the amenorrhea.

Obstetric history with regard to severe postpartum hemorrhage often requiring blood transfusion suggests Sheehan's syndrome leading to hypo-pituitarism and hypo-gonadotropic amenorrhea; manual removal of placenta or severe puerperal sepsis may lead to amenorrhea by causing uterine synechiae (Asherman's syndrome).

Personal history with respect to appetite, diet and caloric intake and exaggerated weight loss/gain may indicate hypothalamic dysfunction (anorexia nervosa or bulimic disorder) as do excessive mental and physical stress and radical life-style changes including exercise pattern. Symptoms related to hypo-estrogenism (hot flushes, mood changes, uro-genital discomfort) should be enquired into in relevant contextual settings.

Central nervous system complaints (headache, seizures, recurrent otherwise unexplained vomiting, visual defects should guide investigations towards the central nervous system; similarly the renal system disorders by causing elevated prolactin levels and inflammatory bowel disease should also not be overlooked. Progressive hirsutism and /or virilisation as reported by the patient should be looked into and may be manifestation of classical late-onset congenital adrenal hyperplasia, androgen-producing ovarian or adrenal tumor. Changes in hair distribution (excessive altered hair growth pattern or thinning or loss of scalp hair or brows should lead the clinician to investigate along the line of thyroid dysfunction or polycystic ovarian disease.

A host of frequently prescribed medications to modern day women can cause hyper-prolactinemia or other central HPO axis dysfunction by altering neuro-transmitter secretion and contribute to amenorrhea. Examples include androgens, oral contraceptive pills, medroxy- progesterone acetate, progestogen intra-uterine systems, GnRH agonists and drugs causing hyper-prolactinemia(phenothiazines, reserpine derivatives, amphetamines, benzodiazepines, anti-depressants, dopamine antagonists, opiates).Table shows commonly prescribed medications which can cause amenorrhea (Table 5)

Group of drug	Names of drugs
Steroid hormones	Oral contraceptive pills, estrogens, progestogens (medroxy - progesterone acetate, progestogen intra -uterine systems), anabo lic steroids, GnRH agonists, androgens
Anti -psychotic drugs	Resperidone
Anti -depressant drugs	Benzodiazepines
Anti -hypertensive drugs	Reserpine derivatives
Anti -allergics	? cetrizine
Cytotoxic agents	Alkylating agents (Busulphan, Cis -platinum Chlora mbucil, Cyclophosphamide, Nitrogen mustardS), Melphalan, , , Procarbazine, , Adriamycin,
Anti -epileptics	Phenobarbitones,phenytoin,carbamazepine,valproic acid
Addiction drugs	Cocaine, opiods, amphetamines
Miscellaneous	Dopamine agonists, cimetidine

Table 5: Medications likely to cause cessation of menstruation

Though amenorrhea ultimately manifests as an abnormality of the reproductive outflow tract, clues as to its cause are often/generally found in other systems like the central nervous system, endocrine system and skin. At the commencement of the examination, the patient's habitus, body mass index and the waist: hip index need to be documented. An obese or asthenic built especially when associated with extreme rapid changes. Notable findings in the skin include its dryness or moistness (thyroid dysfunction), type and distribution of hair (hirsutism, alopecia), acanthosis nigrans, purple stria. Lid lag, exophthalmus and loss of lateral third of brow hair are pointers to thyroid disorders as also fullness in the thyroid region of neck, exaggerated reflexes, full bounding peripheral pulse and fine hand tremors.

Breast development scored on the basis of Tanner's classification should be documented as surrogate markers for estrogen exposure whether natural or exogenous as also advanced breast growth in relation to expected development for biological age, regression in size of previously well-developed breasts, breast striae and the presence and characteristics of any nipple discharge. Purple striae on abdominal skin, buttocks and thighs should be taken note of. A supra-pubic lump could be a hematometra explaining primary amenorrhea or an ovarian tumor causing secondary amenorrhea.

Pattern of sexual hair growth in the infra-umbilical area, the shape of the pubic hair line whether in male escutcheon pattern or not and vulval hair growth levels of circulating androgens and the presence and receptivity of androgen receptors for sexual hair growth. The dimensions of the clitoris, status of the hymen, presence of any transverse septum vaginal and vaginal canalization/atresia need to be systematically documented as indicated by the patient's history. If needed a vaginoscopy with a slender vaginoscope may be done to reveal the presence or absence of a cervix. In a sexually active woman a complete vaginal speculum examination followed by an internal bimanual vaginal examination is to be recorded in a proper format. For those not sexually active per rectal assessment of the uterus and adnexa is carried out.

On the basis of a logical history and a well-conducted systematic physical examination the subsequent workup of the patient can be more directed. In patients who do not demonstrate any obvious etiology the workup should be in a stepwise manner addressing all levels of the HPO axis and the reproductive outflow tract.

The further workup requires blood assays by different modalities and laboratory techniques for hormones related to the HPO axis. Imaging techniques like high-resolution state of art ultrasound, computerized tomography and magnetic resonance imaging look into the normalcy or otherwise of the reproductive outflow tract, ovaries and intra-cranial hypothalamic and pituitary lesions. Often karyotyping and laparoscopy are indicated in order to reach the diagnosis of the cause of amenorrhea.

Investigation modality	Test performed
Biochemistry Laboratory	FSH, LH, estradiol, progesterone, prolactin,auto -immune an tibodies
Microbiology laboratory	PCR for mycobacterium uberculosis
Genetic laboratory	Chromosomal karyotyping, gene studies, FMR -1, Anti - CYP21
Imaging facility	Ultra sound of ovaries and reproductive outflow tract (Antral follicle count -POI, PCOS dis tribution of multiple peripheral small sized cysts) CT scan of hypothalamus and pituitary MRI of hypothalamus and pituitary
Endoscopy	Hysteroscopy Laparoscopy

Table 5: Investigations in evaluating amenorrhea

Tables 6 and 7 indicate the levels of hormones and other relevant clinical findings and investigation findings useful in clinching the etiology responsible for causing amenorrhea.

INVESTIGATING PRIMARY AMENORRHEA

SITE OF DISORDER	DIAGNOSIS	INVESTIGATIONS
HYPOTHALAMUS	Hypothalamic-hypogonadism	FSH, LH and estradiol - Low
PITUITARY	Pituitary adenoma	Prolactin – High FSH, LH and estradiol - Low
OVARY	Gonadal dygenesis (Turner's syndrome)	FSH and LH – High Estradiol – Low Karyotype – 45 XO
MULLERIAN TRACT	Absent uterus (Testicular feminization)	PCT – negative Karyotyping – 46 XY
GENITAL TRACT	Imperforate hymen	FSH, LH, estardiol – normal PCT – negative Examination – imperforate hymen

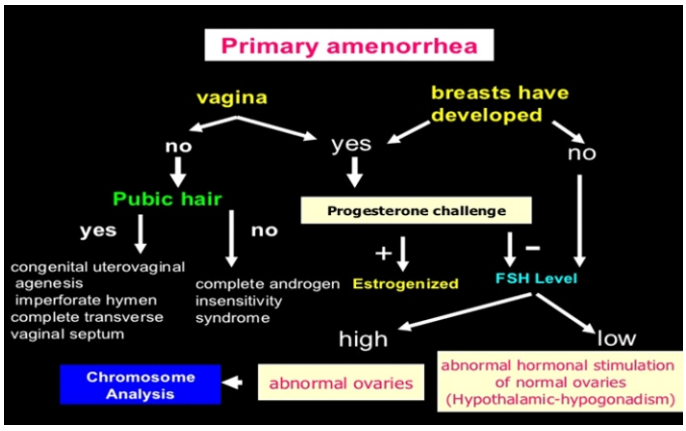
Table 6: Clinical findings and investigations in different causes of primary amenorrhea

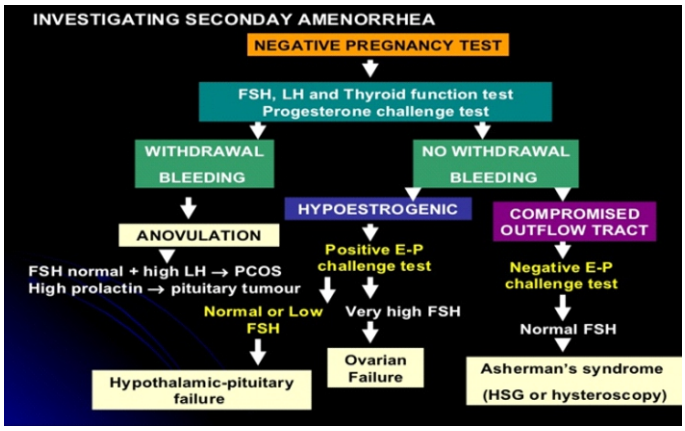
INVESTIGATING SECONDARY AMENORRHEA

SITE OF DISORDER	DIAGNOSIS	INVESTIGATIONS
HYPOTHALAMUS	Hypothalamic – failure Weight-related amenorrhea	FSH, LH and estradiol - Low
PITUITARY	Pituitary adenoma Sheehan syndrome	Prolactin – High FSH, LH and estradiol – Low FSH, LH and estrogen - Low
ENDOCRINE	Hypothyroidism	TSH – raised ; T4 – low or N
OVARY	Premature menopause PCOS	FSH, LH – high ; E_2 – low FSH – Normal ; LH - High
MULLERIAN TRACT	Asherman's syndrome	PCT – negative HSG / Hystereoscopy

Table 7: Clinical findings and investigations in different causes of primary amenorrhea

The following two flowcharts depict the sequence to be followed while examining and investigating cases of primary and secondary amenorrhea.





Treatment depends on the underlying cause delineated by the abovementioned workup protocol. It also takes into consideration the need for regular periods, future reproductive concerns like desire for children or contraceptive intentions of amenorrhea. Figure 4 is a simplified decision making tree summarizing the clinician's approach to a case of amenorrhea.

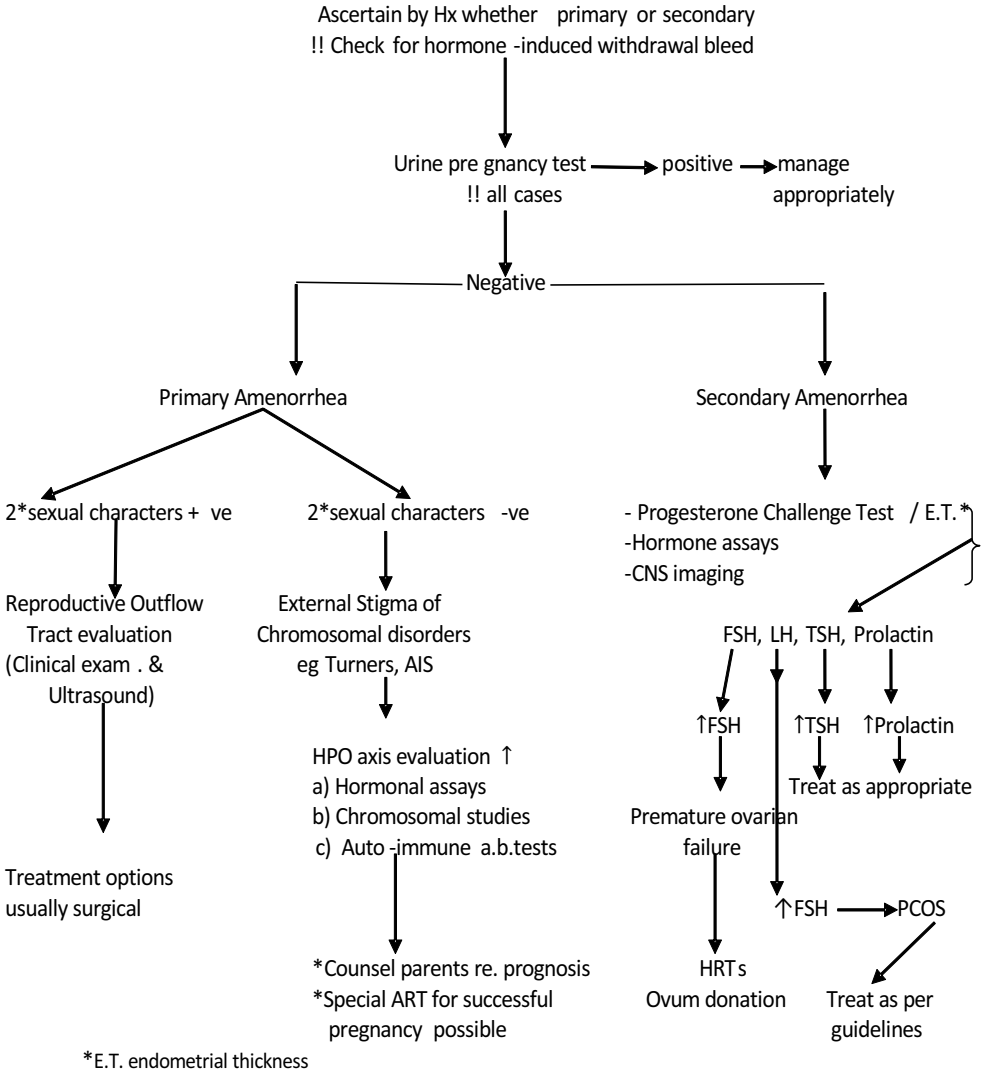


Figure 4: Simplified decision-making tree for evaluating and treating a case of amenorrhea

This opening chapter of FOGSI focus dedicated to the very important and oft-encountered gynecological enigma of amenorrhea with all its attendant issues and concerns orients the reader to the approach which needs to be taken by the caregivers at primary and referral levels when a girl or woman attends for consultation with this presenting complaint. The subsequent chapters individually dilate upon the most important causes which confront the gynecologist. I am confident that readers will find the contained material most useful for themselves in their clinical practice and confidently and rationally manage patients in their individual practice setups.

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2 Hypothalamic and Pituitary Amenorrhea

Dr Suvarna Khadilkar
Dr Firdousara Siddiqui

Introduction

Amenorrhea is a common clinical presentation which needs a thorough work up to pi point the diagnosis. Intact hypothalamo-pituitary ovarian axis (HPO) is essential for normal menstruation. Any dysfunction in the HPO axis or other endocrine glands can lead to amenorrhea. It is also necessary that the reproductive tract is developed fully and normally for normal menstruation.

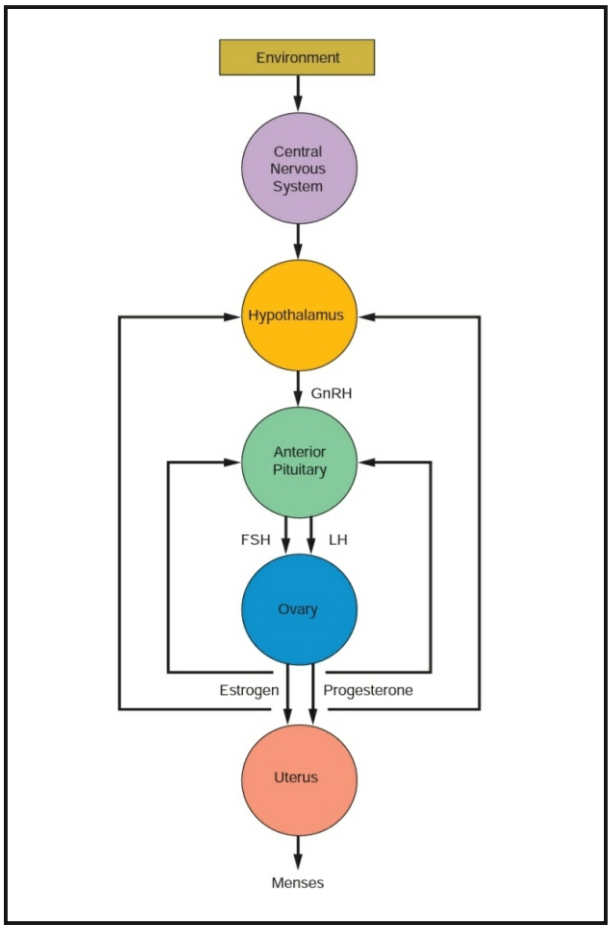
Patient fulfilling any of the following criteria should be evaluated for amenorrhea-

- No menses by age 14 in the absence of growth or development- of secondary sexual characteristics.
- No menses by age 16 regardless of the presence of normal growth and development of secondary Sexual characteristics.
- In women who have menstruated previously, no menses for an interval of time equivalent to a total of at least three previous cycles or no menses over a 6-month period [1].

This chapter will focus on amenorrhea caused by dysfunction or disorders of hypothalamus and pituitary.

Hypothalamic dysfunction is one of the most common causes of Secondary amenorrhea. Secondary amenorrhea, occurs in approximately 3–5 % of adult women. According to the American Society of Reproductive Medicine (ASRM), Functional Hypothalamic Amenorrhea (FHA) accounts for 20–35 % of secondary amenorrhea cases and 3 % of primary amenorrhea [2]. The incidence is higher in athlete women. 50 % of women who exercise regularly experience subtle menstrual disorders and approximately 30 % of women have amenorrhea according to study by DeSouza et al [3]. The female athlete triad first described in 1997 is complex of distorted eating, amenorrhea and osteoporosis [4].

Hypothalamic amenorrhea is diagnosed only after ruling out pituitary and ovarian abnormalities.



Pathophysiological considerations:

Conditions that often precede anovulation include marked weight loss, physical exercise, physical and mental stress, oral contraceptive use. Amenorrhea is usually a result of hypogonadotrophic hypogonadism, marked by low or normal LH, FSH, and estradiol levels. Normal prolactin, and low leptin are also seen in this type of amenorrhea. LH and FSH however do show response to GnRH stimulation.

The cyclic nature of the hormonal changes is at halt, so is the pulsatile secretion of GnRH. Persistent slow frequency of GnRH secretion is inadequate to maintain the level of LH synthesis and secretion required for an ovulatory LH surge, hence leads to anovulation. Extreme physical, nutritional or emotional stress leads to functional suppression of reproduction as a psychobiologic response of life events.

Stress elevates corticotropin-releasing hormone (CRH), which inhibits GnRH secretion and reproductive function in animal studies. Some women with hypothalamic amenorrhea have elevated plasma cortisol levels and blunted responses to CRH, which suggests stress-induced abnormalities in CRH secretion. In women where amenorrhea is associated with strenuous exercise, data suggest a negative energy balance is a precipitating factor, and plasma leptin levels are reduced. Hypoleptinemia appears to be an important factor in athletes and women at low body weight. Administration of recombinant human leptin for 3 months may increase GnRH pulsatility.

Disorders of Hypothalamus and Pituitary Leading to Amenorrhea:

- CNS disorders

-Chronic hypothalamic anovulation
  - Stress
  - Increased exercise levels
  - Anorexia nervosa
  - Pseudocyesis
  - Functional amenorrhea
  - Isolated GnRH deficiency

– Head trauma
– Space-occupying lesions, infections

- Pituitary disorders

– Hyperprolactinemia
  - Prolactinoma
  - Medications
  - PCOS
  - Renal failure

– Hypoprolactinemia
  – Pituitary stalk resection
  – Sheehan's syndrome

Diagnosis and Management :

Detailed personal history with a focus on following points:

Dietary habits, history of eating disorders, exercise and athletic training; attitudes such as perfectionism and desire for social approval; highly ambitious personality, high expectations for self and others, too many weight fluctuations, irregular sleep patterns, stressors, mood fluctuations, menstrual pattern; fractures, and substance abuse.

Clinicians should also obtain a thorough family history with attention to eating and reproductive disorders.

Investigations

Complete blood count, estimation of electrolytes, glucose, bicarbonates blood urea nitrogen, creatinine is recommended. Liver function tests, ESR, C-reactive protein, and basic endocrine work up is also recommended. Basic endocrine work up includes serum thyroid-stimulating hormone, free thyroxine (T4), luteinizing hormone, follicle-stimulating hormone, estradiol, and anti-Mullerian hormone. Androgen levels are advised only when clinical hyperandrogenism is present.

A baseline bone mineral density (BMD) measurement by dual-energy X-ray absorptiometry (DXA) should be obtained with 6 or more months of amenorrhea.

Pelvic ultrasound in all patients to ensure normalcy, and MRI pelvis only when indicated is advised.

Diagnostic tests:

Most commonly performed progesterone challenge test with 10 mg medroxyprogesterone for 5 days is useful to differentiate between ovarian cause and hypothalamic cause. If withdrawal period is achieved, then it denotes presence of endogenous estrogen and ensures outflow tract function and patency. There will be no withdrawal period if there is no endogenous estrogen present like in hypothalamo-pituitary causes.

Following tests are used only when the diagnosis cannot be made with routine clinical examination and investigations.

1. GnRH stimulation test: this is of use to differentiate between hypothalamic and pituitary causes of hypogonadism.100 µg GnRH is given intravenously. LH and FSH response is measured with samples at 0, 20 and 60 minutes In pituitary disease, response is either absent or blunted. In hypothalamic disease, normal response is seen.

2. Clomiphene stimulation test may be useful to distinguish organic causes of gonadotropin deficiency (pituitary or hypothalamic pathology)

from functional disorders and idiopathic delayed puberty. In healthy adults, clomiphene blocks estrogen feedback mechanisms in the hypothalamus, thus leading to a rise in GnRH (gonadotropin-releasing hormone) and consequently circulating LH and FSH. After 7 days of clomiphene stimulation, if LH levels increase more than 120% and FSH increases more than 40 %, the response is considered normal. A normal response essentially rules out organic causes of hypogonadotropic hypogonadism and in delayed puberty, it is an indication that sexual maturity will ensue.

3. In hypothalamic-pituitary pathology there is no response. Not useful in girls with early puberty.To differentiate between functional and organic cause of amenorrhea, some form of imaging of the brain (CT or MRI) to rule out a tumor may be useful especially when a history of severe or persistent headaches; persistent vomiting, unexplained change in vision, thirst, or urination, lateralizing neurologic signs, and any indication of pituitary hormone deficiency or excess.

Treatment :

General principles :

• For acute and morbid patients inpatient therapy is required

• Correcting the energy imbalance is important

• If nutritional, psychological, and modified exercise intervention (Cognitive behavior therapy CBT) are not effective, oral contraceptive pills for maintenance of menstrual cycles and Bone mineral density are required.

• Bisphosphonates, denosumab, testosterone, and leptin are not recommended [5]

• If CBT is not effective, treatment with pulsatile gonadotropin-releasing hormone (GnRH) as a first line, followed by gonadatropin therapy and induction of ovulation, is used for treatment of infertility.

Eating disorders :

Cultural influences, other psychological, biologic, genetic and social factors likely contribute to development of eating disorders. Peripubertal girls and young women having first degree relatives with an eating or affective disorder or alcoholism are at increased risk of developing eating disorder. The susceptibility is identified on loci for Anorexia nervosa on chromosome 1 and for bulimia nervosa on Chromosome 10.

Two types of Anorexia nervosa have been defined restricting and binge/purging. The diagnostic Criteria for bulimia nervosa are distinct from those for anorexia nervosa primarily in that they do not include low body weight or amenorrhea.

The weight loss due to any reason will result in reduction in total percentage of fat in the body. 22% of body fat is the critical body fat percentage necessary for sustaining menstruation. If this percentage drops below 22% then the amenorrhoa or the menstrual dysfunction results. Anorexa nervosa patients exhibit hypercortisolism due to increased corticotropohin releasing hormone [CRH}and ACTH. CRH directly inhibits GnRh secretion through increased endogenous opioids hence leads to speroff's compartment IV amenorrhoea. Brain senses the blood levels of leptin If weight loss is due to excessive physical exercise, it is found that the athletes have 3 fold lower levels of leptin .therefore even athletes have amenorrhoea.

Sometimes those suffering with anorexia or bulimia do not appear underweight. Some may be of average weight or slightly overweight. Variations can be anywhere from extremely underweight to extremely overweight. The appearance of a person suffering with an eating disorder does not dictate the amount of physical danger they are in, nor does it determine the severity of emotional conflict they are enduring.

Prevention and identification of early or partial disorder to prevent full blown syndrome is important.

Diagnosis is usually clinical but GnRH levels close to zero in presence of high levels of cortisol differentiate this disorder from pituitary insufficiency. Weight loss due to other endocrine or other diseases may be misdiagnosed and vice versa.

Complications:

Patient with anorexia nervosa are at risk for many complications related to nutritional and electrolyte imbalances Amenorrhea Anovulation Neuropathies

Myopathies Life-threatening cardiac arrhythmias, Gastritis, Esophagitis, Weakness from chronic anemia.
The most common cause of death in anorexia nervosa is suicide.

Treatment:
Management requires a team approach in which different professionals work together. Individual and family psychotherapy are effective in patients with anorexia nervosa and cognitive-behavioral therapy is effective in bulimia nervosa.

Care of patients with anorexia nervosa includes stabilization for any life-threatening conditions (eg, shock, cardiac arrhythmias). In addition, protection of the patient may be necessary if risk of suicide is present. Treatment may include rehydration, correction of electrolyte abnormalities (eg, hypokalemia), and institution of appropriate disposition for continuing medical and psychiatric treatment. Consultation with psychiatry and adolescent medicine specialists in order to optimize inpatient care and facilitate outpatient follow-up care should be done.

For nutritional therapy, forced feedings with total parenteral nutrition or tube feedings provide nutrients, stabilize nutrient deficiency syndromes, and alter mood when the patient becomes nutritionally replenished. Preliminary treatments with opiate antagonists have shown promising results. Monitoring of nutritional status (eg, serum protein and albumin, electrolytes, serum glucose) is important. As nutritional status improves, outpatient treatment can be offered. Daily caloric intake 2600 cal /day is advised. Ongoing psychiatric care is necessary, as the relapse rate is high.

Prognosis:
• The general prognosis is related to the severity of the underlying personality and family psychopathology.
• The prognosis for patients with a bulimic component is worse than for those without bulimia. Death for patients with bulimia is 5-40%.
A small percentage of patients become symptom free, 30% remain chronically ill, and the rest are vulnerable to the return of symptoms during stressful times .

Eating disorders are relatively rare in India but may be picked up more often if actively looked for. Active search may help early diagnosis, as well as effective treatment and will reduce high mortality associated with it. Change of lifestyle, psychological counseling of not only the peripubertal girls but also of their disturbed family is important.

Stress or exercise induced amenorrhea:
Women who are involved in strenuous recreational exercise or other forms of demanding physical activity such as dancing have a high prevalence of menstrual irregularity and amenorrhea.[3] The potential adverse effect of intense exercise and low body weight on menstrual function is synergistic.

Exercising amenorrheic women do not exhibit a normal diurnal leptin rhythm; treatment with exogenous recombinant human leptin can restore gonadotropin pulsatality, follicular development and ovulatory function in exercising amenorrheic women.[4]

Congenital GnRH deficiency (normosmic) is seen in rare individuals, congenital specific mutation that prevents normal GnRH neuronal migration during embryogenesis or to mutation in the pituitary GnRH receptor.

Kallmann Syndrome is Congenital GnRH deficiency associated with anosmia or hyposmia the disorder is known as Kallmann Syndrome, classical X linked disorder, caused by genetic mutation in the KAL gene. Kallmann syndrome can be inherited in autosomal dominant or recessive fashion.

GnRH Receptor Mutations- There are more than 20 inactivating mutations in the GnRH receptor gene (GNRHR). Some results in interference with normal Signal transduction, some effectively prevent GnRH binding, both results in resistance to GnRH stimulation.

Disorder of Anterior Pituitary
Variety of disorder involving anterior pituitary may cause amenorrhea ,most common by far is benign Adenomas, Other include craniopharyngioma, meningiomas, gliomas, metastatic tumors and chondromas.

Pituitary adenomas are classified by cell type and size and may be functional (hormone secreting) or nonfunctional. Tumors less than 10mm in size are called microadenomas and those 10mm or larger are called macroadenomas. Pituitary adenomas may be incidentally diagnosed while evaluating for neurological Symptoms or workup of menstrual irregularities The most common neurological symptoms associated with pituitary tumors, macroadenomas is visual impairment, classically Bitemporal hemianopsia, other symptoms include decreased visual acuity, diplopia, headache, CSF rhinorrhea, pituitary apoplexy.

Pituitary adenomas (Prolactinoma) are treated with Dopamine agonist bromocriptine, Drug of choice and recommended dose is 1.25mg at bedtime daily for the first week and then gradually increased. Other promising drug is cabergoline given in dose of 0.25mg once or twice weekly till tumors shrink, transsphenoidal resection of tumor is done if medical therapy fails.

Sheehan Syndrome

Necrosis of the pituitary following postpartum hemorrhage may lead to Sheehan syndrome. Syndrome may develop slowly over 8–10 years' time. The hormones like GH, FSH and LH, TSH and ACTH are reduced. Initially failed lactation can be the presenting symptom. Secondary amenorrhea and loss of secondary sexual characteristics are seen in most cases. Replacement of deficient hormones is necessary in majority of cases to maintain quality of life.

Inappropriate secretion of prolactin (including drugs, other diseases, e.g. hypothyroidism, prolactinoma) will affect secretion of LH and FSH.

GnRH stimulation test differentiates between hypothalamic and pituitary cause of hypogonadism. Clomiphene stimulation test distinguishes organic cause of gonadotropin deficiency from functional disorder and idiopathic delayed puberty. Clomiphene blocks estrogen feedback mechanism in hypothalamus, normal response rules out hypogonadotropic hypogonadism and delayed puberty, no response is seen in hypothalamus-pituitary pathology, diagnosis of functional disorder is made by CT or MRI imaging.[6]

Conclusion:

Hypothalamic and pituitary Amenorrhea is an underestimated clinical problem. It is related to profound impairment of reproductive functions including anovulation and infertility. Women's health in this disorder is disturbed in several aspects including their skeletal system, cardiovascular system and mental problems. Patients manifest a decrease of bone mass density, which is related to an increase of fracture risk. Therefore, osteopenia and osteoporosis are the main long-term complications of Hypothalamic Amenorrhea. Cardiovascular complications include endothelial dysfunction and abnormal changes in the lipid profile. Hypothalamic Amenorrhea patients present significantly higher depression and anxiety and also sexual problems compared to healthy subjects.

Amenorrhea patients should be carefully diagnosed and properly managed to prevent both short- and particularly long-term medical consequences.

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3

Amenorrhoea: Endocrine Issues

Dr Pratik Tambe

Background

The recognition that rhythmic production of oestrogen and progestogen by the ovary is central to the cycle of follicular ripening, ovulation, corpus luteum formation, degeneration and menses has been part of medical science since centuries and is affirmed in medical texts. The pathological issues surrounding amenorrhoea including congenital and acquired disease of the ovary, faulty ovarian development, genetic issues and sex reversal, hyperandrogenism and polycystic ovary syndrome have all been dealt with in publications since over 50 years ago.1

Aetiology

The commonly encountered causes of amenorrhoea can be categorised as outflow tract abnormalities, primary ovarian insufficiency, hypothalamic and pituitary disorders, neuroendocrine issues and sequelae of many chronic disease.

Outflow tract abnormalities	**Hypothalamic or pituitary disorders** *(continued)*	**Other endocrine gland disorders**
Acquired	Constituional delay of puberty	Adrenal insufficiency
Cervical stenosis	Empty sella syndrome	Androgen-secreting tumor (e.g., ovarian or adrenal)
Intrauterine adhesions	Functional (overall energy deficit or stress)	Cushing syndrome
Congenital	Eating disorder	Diabetes mellitus, uncontrolled
5α-reductase deficiency	Stress	Late-onset congenital adrenal hyperplasia
Androgen insensitivity syndrome	Vigorous exercise	Polycystic overy syndrome (multifactorial)
Imperforate hymen	Weight loss	Thyroid disease
Műllerian agenesis	Gonadotropin deficiency (e.g., Kallmann syndrome)	**Amenorrhea attributed to chronic disease**
Transverse vaginal septum	Hyperprolactinemia	Celiac disease
Primary ovarian insufficiency	Adenoma (prolactinoma)	Inflammatory bowel disease
Acquired	Chronic kidney disease	Other chronic disease
Autoimmune	Medications or illicit drugs (e.g., antipsychotics, opiates)	Physiologic or induced
Chemotherapy or radiation	Physiologic (pregnancy, stress, exercie)	Breastfeeding
Congenital	Infarction (e.g., Sheehan syndrome)	Contraception
Gonadal dysgenesis (other than Turner syndrome)	Infiltrative disease (e.g., sarcoidosis)	Exogenous androgens
Turner syndrome or variant	Infectio (e.g., meningitis, tuberculosis)	Menopause
Hypothalamic or pituitary disorders	Medications or illicit drugs (e.g., cocaine)	Pregnancy
Autoimmune disease	Trauma or surgery	
Brain radiation	Tumor (primary or metastatic)	

Table 1 Spectrum of disorders presenting with amenorrhoea[2]

Clinical findings

A detailed history and thorough clinical evaluation is a must though with the advent of new diagnostic methodologies in our armamentarium, this is sometimes ignored. The history should include menstrual onset and patterns, breast and pubic hair development, eating and exercise habits, presence of psychosocial stressors, body weight changes, medication use, galactorrhoea and any chronic illness. Additional questions may target neurologic, vasomotor, hyperandrogenic or thyroid-related symptoms.

The physical examination should identify anthropometric and pubertal development trends. All patients should be offered a pregnancy test and assessment of serum follicle-stimulating hormone, luteinising hormone, prolactin, and thyroid-stimulating hormone levels. Additional testing, including karyotyping, serum androgen evaluation and pelvic or brain imaging should be individualised.[2,3,4]

Findings	Associations
History	
Chemotherapy or radiation	Impairment of specific organ or structure, (e.g., brain, pituitary, ovary)
Family history of early or delayed menarche	Constitutional delay of puberty
Galactorrhea	Pituitary tumor
Hirsutism, acne	Hyperandrogenism, PCOS, ovarian or adrenal tumor, CAH, Cushing syndrome
Illicit or prescription drug use	Multiple associations, consider effect on prolactin
Loss of smell (anosmia)	Kallman syndrome (GnRH deficiency)
Menarche and menstrual history	Primary vs. secondary amenorrhea
Sexual activity	Pregnancy
Significant headaches or vision changes	Central nervous system tumor, empty sella syndrome
Temperature intolerance, palpitations, diarrhea, constipation, tremor, depression, skin changes	Thyroid disease
Vasomotor symptoms (e.g., hot flashes or night sweats)	Primary overian insufficiency, natural menopause
Weight loss, excessive exercise, poor nutrition, psychosocial distress, diets	Functional hypothalamic amenorrhea
Physical examination	
Abnormal thyroid examination	Thyroid disorder
Acanthosis nigricans or skin tags	Hyperinsulinemia (PCOS)
Anthropomorphic measurements; growth charts	Multiple associations; Turner syndrome, constitutional delay of puberty
Body mass undex	High: PCOS Low: Functional hypothalamic amenorrhea
Bradycardia	Functional hypothalamic amenorrhea (e.g., anorexia nervosa)
Breast development (normal progression)	Presence of circulating estrogen*
Dysmorphic features (e.g., webbed neck, short stature, low hairline)	Turner syndrome
Male pattern baldness, increased facial hair, acne	Hyperandrogenism, PCOS, ovarian or adrenal tumor, CAH, Cushing syndrome
Pelvic examination	
Absence or abnormalities of cervix or uterus	Rare congenital causes including Müllerian agenesis or androgen insensitivity syndrome
Clitoromegaly	Androgen-secreting tumor; CAH; 5α- reductase deficiency
Presence of transverse septum or imperforate hymen	Outflow tract obstruction
Reddened or thin vaginal mucosa	Decreased endogenous estrogen
Sexual maturity rating abnormal	Turner syndrome, constitutional delay of puberty, rare causes
Striae, buffalo hump, central obesity, hypertension	Cushing syndrome

Table 2 Pathognomonic findings on clinical examination[2]

Investigations

These should be tailored to the differential diagnosis after history and clinical examination. While a battery of tests is often ordered to ensure that no diagnosis is missed, the socioeconomic status of the patient should be taken into consideration so that we do not over-burden the patient.

Findings	Associations
Laboratory testing (refer to local reference values)	
17-hydroxyprogesterone level (collected at 8 a.m.)	High: late-onset CAH
Anti-Müllerian hormone	High: Functional hypothalamic amenorrhea, PCOS Low: Primary ovarian insfficiency
Complete blood count and metabolic panel	Abnormal: chronic disease (e.g., elevated liver enzymes in functional hypothalamic amenorrhea)

Findings	Associations
Estradiol	Low: Poor endogenous estrogen production (suggestive of poor current ovarian function)
Follicle-stimulating hormone and luteinizing hormone	High: Primary ovarian inssufficiency; Turne syndrome Low: Functional hypothalamic amenorrhea Normal: PCOS; intrauterine adhesions; multiple others
Free and total testosterone; dehydroepiandrosterone sulfate	High: Hyperandrogenism, PCOS, ovarian or adrenal tumor, CAH, Cushing syndrome
Karyotype	Abnormal: Turner syndrome, rare chromosomal disorders
Pregnancy test	Positive: Pregnancy, ectopic pregnancy
Prolactin	High: Pituitary adenoma, medications, hypothyroidism, other neoplasm
Thyroid-stimulating hormone	High: Hypothyroidism Low: Hyperthyroidism
Radiographic testing	
Dual energy x-ray absorptiometry	Evaluation of fracture risk
MRI of the adrenal glands	Androgen-secreting adrenal tumor
MRI of the brain (including sella)*	Tumor (e.g., microadenoma)
Pelvic organ ultrasonography or magnetic resonance imaging	Morphology of pelvic organs, polycystic ovarian morphology, androgen-secreting ovarian tumor

Table 3 A Snapshot of investigations in amenorrhoea[2]

While ordering a multitude of investigations is quite easy and commonplace in modern practice, having the appropriate clinical knowledge to interpret them is equally important. A multidisciplinary team approach is also important to ensure that the diagnosis is not missed.

	17-OHP	AMH	DHEA-S	Estradiol	LH (IU per L)	LH/ FSH	FSH (IU per L)	Prolactin	Testosterone	TSH
Congenital adrenal hyperplasia	High	Normal	High normal	Low	< 15	> 1	< 10	Normal	High	Normal
Functional hypothalamic amenorrhea	Normal	High	Normal	Low	< 10†	~ 1	< 10†	Low normal	Low normal	Low normal
Hyperprolactinemia	Normal	Normal	Normal or slightly high	Low	< 10	> 10	< 10	High	Normal	High normal
Menopause	Normal	Low	Normal	Low	< 15	< 1	>15	Normal	Low normal	Normal
Polycystic ovary syndrome	Normal	Normal of high	High normal	Low	< 15	> 1	< 10	High normal	High or high normal	Normal
Primary ovarian insufficiency	Normal	Low	Normal	Low	< 15	< 1	> 15	Normal	Low normal	Normal

Table 4 Interpreting hormonal investigations in amenorrhoea[2]

Primary ovarian insufficiency

Primary ovarian insufficiency affects approximately one in 100 women and is defined by follicle dysfunction or depletion and two serum FSH levels in the menopausal range obtained at least one month apart. Vasomotor symptoms and vaginal dryness are common. Most cases are idiopathic; however, irradiation, chemotherapy, infections, tumors, autoimmune processes, and chromosomal irregularities can also cause primary ovarian insufficiency. A karyotype is abnormal in approximately one-third of patients and it should be offered to all patients with this diagnosis to identify Turner syndrome or its variants.[5]

Hormone replacement therapy (HRT) may reduce associated vasomotor symptoms, bone mineral density loss and cardiovascular risk and should be continued until the age of natural menopause. A common post-pubertal regimen of HRT is 100 mcg of daily transdermal estradiol or 0.625 mg of daily oral conjugated estrogens, adding 200 mg of micronised oral progesterone daily for 12 days each month. Transdermal estrogen may be associated with lower venous thromboembolism risk than oral formulations. It is also recommendedto add 1,200 mg of calcium daily and 1,000 IU of vitamin D daily withregular weight-bearing exercises to maintain bone mineral density in accordance with guidelines for postmenopausal women.

Functional hypothalamic amenorrhoea (FHA)

FHA, or stress-induced anovulation, is one of the most common causes of secondary amenorrhea and accounts for the reproductive dysfunction seen in under-nutrition, excessive exercise, severe emotional stress and chronic disease. From an evolutionary standpoint, it is adaptive for an animal to allocate energy resources for its own survival rather than reproduction in the face of nutritional or physical stress. Therefore, FHA is a physiological response to environmental and physical stressors.[7]

During periods of physical, nutritional, or extreme emotional stress, the hypothalamo-pituitary-adrenal (HPA) axis is activated and inhibits the HPO axis at multiple levels. At the level of the hypothalamus, CRH suppresses GnRH secretion. At the level of the pituitary, ACTH has been shown to have negative reproductive effects. Women with FHA also have higher 24-hour mean plasma cortisol levels which suppresses reproductive function at the hypothalamic, pituitary and uterine levels.

Women with Cushing's disease and women on long-term supra-physiological prednisolone therapy have a reduced LH response to GnRH, thus suggesting that glucocorticoids also suppress the responsiveness of pituitary gonadotrophs to hypothalamic input. Glucocorticoids also inhibit the effects of estradiol on the uterus. Thus, a cross-talk between the HPA and HPO axes promotes the development of amenorrhea as a functional adaptation to stress.[8]

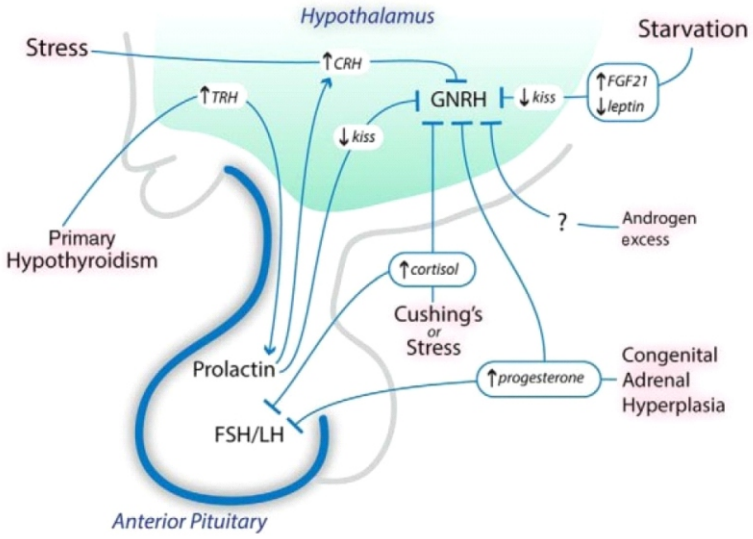

Fig 1 Neuroendocrine regulation mechanisms

FHA is a diagnosis of exclusion and evaluation typically reveals low or low-normal serum-luteinizing hormone and follicle-stimulating hormone levels and low serum estradiol. Low levels of leptin, low insulin levels, high FGF-21 and low kisspeptin levels are all seen in FHA. Bone mineral density testing should be considered after six months of amenorrhea, severe nutritional deficit, or history of stress fracture.

Treatment should correct the underlying cause to restore ovulatory function through behaviour change, nutritional repletion, stress reduction, and weight gain. A multidisciplinary team including a clinician, nutritionist or registered dietician and therapist may be optimal. Patients with severe bradycardia, hypotension, orthostasis, or electrolyte abnormalities may require inpatient treatment.[9]

Hyperprolactinaemia

Elevated serum prolactin may induce amenorrhea by inhibiting gonadotrophs.Pregnancy and lactation are the important differential diagnoses which need to be excluded. Hyperprolactinaemic women have reduced LH-pulsefrequency and reduced LH responsiveness to estrogen with GnRH suppression. Common causes include medication use (antipsychotics), pregnancy and pituitary adenomas. Most patients with elevated serum prolactin and those refractory to medical treatment will require MRI of the pituitary.Symptomatic prolactinomas may be treated with dopamine agonists or resection.

Lactotroph adenomas

Prolactin-secreting adenomas (lactotroph adenomas) are the most common subtype of secretory pituitaryadenoma. These tumours are usually benign and prolactin levels typically correlate with tumour size.Individuals with large adenomas can have prolactin levels on the order of 10 ng/mL, yet with poorlydifferentiated or cystic lesions, prolactin levels will be lower than expected based on size.[10,11]

Stalk disruption and sellar masses

Dopamine is produced by neurons in the arcuate nucleus of the hypothalamus and tonically suppressespituitary prolactin production. Any disruption of the stalk connecting the hypothalamus to the pituitary canprevent the flow of dopamine into the pituitary gland and result in hyperprolactinemia and amenorrhoea.

Any sellar mass or lesion can cause amenorrhea via hyperprolactinemia due to stalk disruption and/or compression of the pituitary gonadotrophs, particularlywhen the lesion is ≥ 1 cm. In the case of functioning adenomas, hormonal effects may also play a role inthe development of amenorrhoea.

Primary hypothyroidism

TRH secreted by the hypothalamus, stimulates release of TSH by the pituitary and also stimulatesprolactin release. Women with primary hypothyroidism have a heightened prolactin response toTRH, resulting in greater prolactin secretion in response to TRH stimulation leading to hyperprolactinemia and resultant amenorrhoea.Primary hypothyroidism may also lead to significant enlargement of the pituitary gland due to thyrotrophand lactotroph hyperplasia, but treatmentof hypothyroidism should result in regression ofthe hyperplasiaand normalisation of the prolactin levels.[12,13]

Cushing's disease

Amenorrhea is a common finding in women with ACTH-secreting adenomas (Cushing's disease). Cushing's disease is associated with amenorrhoea, higher mean serum cortisol levels and lower estradiol and SHBG levels. Amenorrhea in Cushing's disease is more likely mediated bysuppression of GnRH by cortisol rather than hyperandrogenaemia.[14]

Acromegaly

Amenorrhea and infertility are also common findings in women with GH-secreting adenomas(acromegaly). Amenorrhoea is associated withhigher GH levels and lower LH and estradiol levels. As with any sellar mass, compression of pituitarygonadotrophs, or hyperprolactinemiadue to secretion of prolactin by the tumour or stalkdisruptionmay result in the development of amenorrhoea. Another potential cause may beincreased androgen bioavailability due to decreased SHBG levels.[15]

Rare conditions

Thyrotroph adenomas, chest wall injury, chronic renal failure, metastatic infiltration, hypophysitis, granulomatous disease like sarcoidosis, haemochromatosis, Langerhans cell histiocytosis, traumatic brain injuries, radiation etc. all represent rarer issues disrupting the HPA axis.

Sheehan's syndrome

During pregnancy, the pituitary gland enlarges due to estrogen stimulation of lactotroph cells. This enlarging tissue may compress the superior hypophyseal artery, making the and vulnerable to changes in blood supply. Women with significant postpartum haemorrhage may develop ischaemic necrosis of the pituitary gland, resulting in hypopituitarism.

Sheehan's syndrome is now less commonly seen in developed countries due to improvements in PPH management; however, recent reports suggest that its incidence in the developed world may be greater than previously thought. A retrospective study from France demonstrated a mean delay of 9 years before diagnosis, suggesting that the diagnosis is often overlooked in developed countries.[16,17]

Idiopathic hypothalamic amenorrhoea

IHH is a heterogeneous group of disorders where there is delayed or absent pubertal development—typically due to GnRH deficiency or a GnRH receptor mutation— coupled with normal anatomical findings on hypothalamic/pituitary imaging.

The typical presentation is primary amenorrhoea. The associated phenotypic findings include anosmia (Kallman's syndrome). Genetic mutations that impair neuronal migration commonly result in concurrent hypogonadism and anosmia due to the shared embryonic development of GnRH and olfactoryneurons. These include mutations in the KAL1 gene, the FGF-1 receptor, FGF-8, the gene encoding semaphorin-3A, the CHD7 gene and the genes encoding prokineticin-2 and prokineticin receptor-2.

Genetic defects in GnRH secretion and function have also been identified in cases of IHH with normosmia. Kisspeptin is a potent regulator of GnRH secretion and mutations in KISS1 and KISS1R, the genes encoding kisspeptin and its receptor, cause hypogonadism. Mutations of the gene encoding leptin, its receptor and mutations in the pro hormone convertase 1 gene, GnRH receptor mutations have all been associated with both hypogonadotropic hypogonadism and severe obesity.

Unlike most patients with IHH, individuals with GnRH receptormutations typically do not respond to conventional doses of pulsatile GnRH administration, althoughsuccessful conception with high-dose pulsatile GnRH has been reported. The underlying mutations may confersusceptibility to the development of FHA.[18,19,20]

Congenital adrenal hyperplasia (CAH)

CAH is a family of inherited disorders characterised by defects in cortisol production, resultingin increased ACTH production due to reduced negative feedback and consequent adrenal glandproliferation. Although there are rare forms of CAH that result in infertility, including 11β-hydroxylasedeficiency, 17α-hydroxylase deficiency and 3β-hydroxysteroid dehydrogenase deficiency, CAHmost commonly arises from autosomal recessive mutations in the gene that encodes 21-hydroxylase - (21-OH), CYP21A2, which result in shunting of steroid precursors toward androgen biosynthesis.

There isconsiderable variability in disease phenotype, depending on the severity of the mutation. Classical 21-OHdeficiency is typically diagnosed at birth and can present with severe salt wasting and/or prenatalvirilisation of external female genitalia, whereas non-classical CAH (NC21OHD) presents with signs of hyperandrogenism including hirsutism, acne, frontalbalding, and menstrual irregularities.

The oligomenorrhea in women with 21-OH deficiency is likely due to elevated androgen and/orprogesterone levels. Patients with classic 21-OH deficiency with irregular menstrual cycles have elevatedprogesterone and androstenedione levels that are associated with reduced LH-pulse amplitude andfrequency. The exact mechanism by which androgens act to induce oligomenorrhea is unknown, but hyperandrogenaemia may be a contributing factor in CAH. Elevated levels of progesterone, a substrate of21-OH, also likely contribute to menstrual irregularity.

Although classical CAH is relatively rare, NC21OHD is one of the most common autosomal recessivediseases known, occurring in 1 in 100 individuals in a mixed ethnic population and at a

much higherfrequency (1 in 27) in the Ashkenazi Jews. It isimportant to distinguish NC21OHD from other causes of hyperandrogenism and oligomenorrhea, such aspolycystic ovary syndrome.

The most definitive hormonally based diagnostic test for NC21OHD is ACTHstimulation test measuring serum concentrations of 17-hydroxyprogesterone (17-OHP), a substrate of 21-OH, afterACTH administration. Patients with NC21OHD have stimulated 17- hydroxyprogesterone levels thatare intermediate between normal subjects and those with classical 21-OH deficiency.[21,22,23]

Management pathways and algorithms

We present two simplified pathways for investigating and treating primary and secondary amenorrhoea, with particular attention to the endocrine issues surrounding this condition.

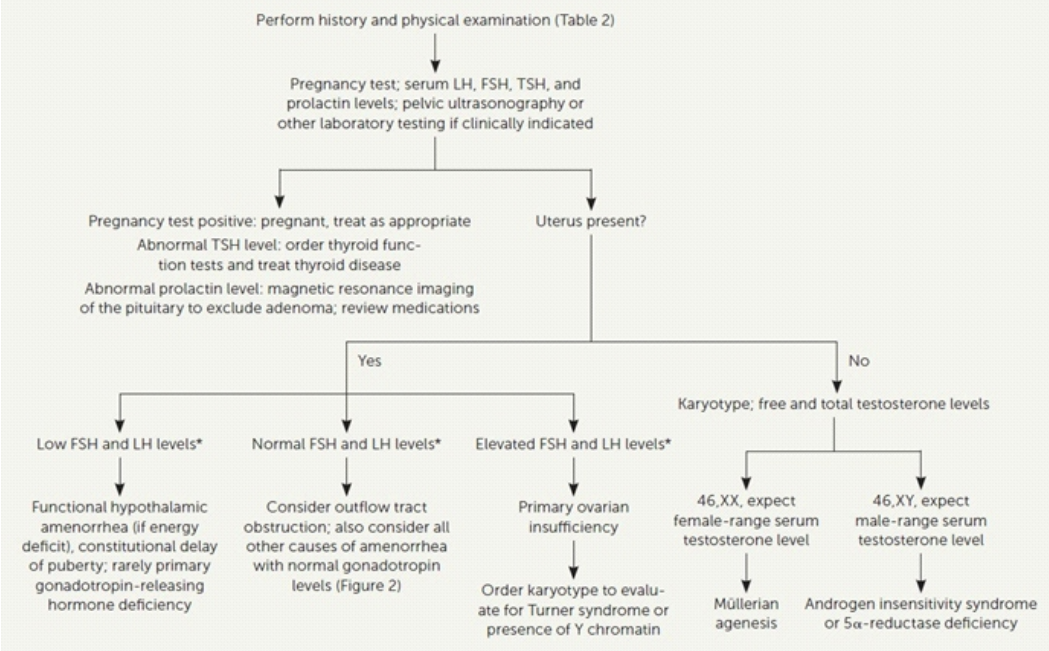

Fig 2 Evaluation of primary amenorrhoea[2]

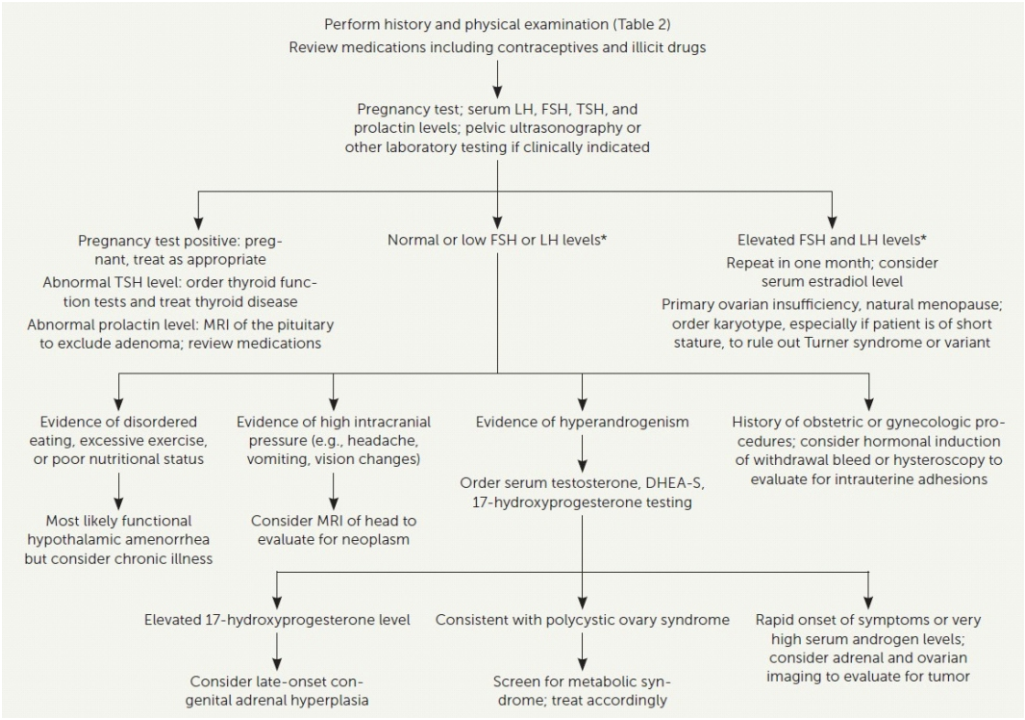

Fig3Evaluation of secondary amenorrhoea[2]

Conclusions

In conclusion, physiological, pathological and iatrogenic causes contributing to disruption of the HPA and HPO axes constitute a majority of cases of amenorrhoea and infertility. Functional hypothalamic amenorrhoea, a physiological response to physical, emotional or nutritional stress is the most common cause of neuroendocrine amenorrhoea and identifyingthis entity is essential in order to diagnose and treat the underlying disorder. Given the consequences of nottreating amenorrhea, viz., loss of bone mass and fertility issues, prompt diagnosis and institution of treatment is critical.

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4

Hyperprolactinemia : Management Update

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Abstract

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis. It presents as an ovulatory disorder and is often associated with secondary amenorrhea or oligomenorrhea, galactorrhea and osteopenia. When hyperprolactinemia is confirmed, a cause for the disorder needs to be sought. This involves a careful history and examination, followed by laboratory tests and diagnostic imaging of the sella turcica. Dopamine agonists are the treatment of choice for the majority of patients. Cabergoline has been shown to be more effective and better tolerated than bromocriptine. Transsphenoidal surgery is usually reserved for patients who are intolerant or resistant to dopamine agonists or when hyperprolactinemia is caused by non-prolactin-secreting tumors compressing the pituitary stalk.

Introduction

Prolactin is a pituitary-derived hormone that plays a pivotal role in a variety of reproductive functions. It negatively modulates the secretion of pituitary hormones responsible for gonadal function including luteinizing hormone(LH)and follicle-stimulating hormone(FSH).Hyperprolactinemia is a condition of elevated prolactin levels in blood which could be physiological, pathological, pharmacological or idiopathic in origin. Management depends on the cause and on the effects it has on the patient.In this review we summarize advances in our understanding of the clinical significance of hyperprolactinemia and its management.

Regulation of Prolactin secretion

Prolactin is a 198-amino acid protein (23-kd) produced in the lactotroph cells of the anterior pituitary gland. Its primary function is to enhance breast development during pregnancy and to induce lactation. Prolactin is under dual regulation by hypothalamic hormones delivered through the hypothalamic–pituitary portal circulation. Under most conditions the predominant signal is inhibitory, preventing prolactin release and is mediated by the neurotransmitter dopamine. The stimulatory signal is mediated by the hypothalamic hormone thyrotropin-releasing hormone. The balance between the two signals determines the amount of prolactin released from the anterior pituitary gland and the amount cleared by the kidneys influences the concentration of prolactin in the blood. (1,2)

Epidemiology

The occurrence of clinically apparent hyperprolactinemiadepends on the study population and occurs in less than 1% of the general population (3).The rate is higher among patients with specific symptoms that may be attributable to hyperprolactinemia. Its incidence is estimated at 9% among women with amenorrhea, 25% among women with galactorrhea and as high as 70% among women with amenorrhea and galactorrhea.(3) 17 % PCOS patients present with hyperprolactinemia. Of these patients, approximately 30% have prolactin-secreting tumors.The prevalence is about 5% among men who present withimpotence or infertility.(4)

ETIOLOGY

The diagnosis of hyperprolactinemia should be suspected in female patients presenting with oligomenorrhea, amenorrhea, galactorrhea, or infertility. Hyperprolactinemia can be physiological or pathological. Some of the common causes are listed in Figure 1(5)

Prolactinomas account for 25-30% of functioning pituitary tumors and are the most frequent cause of chronic hyperprolactinemia.[6] Prolactinomas are divided into two groups: (i) Microadenomas (smaller than 10 mm) which are more common in premenopausal women and (ii) Macroadenomas (10 mm or larger) which are more common in men and postmenopausal women.

Clinical presentation

Clinical presentation in women is more obvious and occurs earlier than in men. They typically present with oligomenorrhea, amenorrhea, galactorrhea, or infertility(7-9). Galactorrhea is less common in postmenopausal women due to lack of estrogen.[3]

Physiological	Pathological
Coitus Exercise Lactation Pregnancy Sleep Stress	Hypothalamic -pituitary stalk damage Granulomas Infiltrations/Irradiation Trauma: pituitary stalk section, suprasellar surgery Tumors: cranio -pharyngioma hypothalamic me tastases, meningioma, suprasellar pituitary mass extension Pituitary Prolactinoma Acromegaly Macroadenoma (compressive) Macroprolactinemia Surgery * Trauma
Pharmacological	**Systemic disorders**
Anesthetics Anticonvulsant Antidepressants Antihistamines (H2) Antihypertensives Do pamine receptor blockers Estrogens: oral contraceptives; Neuroleptics/antipsychotics Opiates and opiate antagonists	Hypothyroidism Polycystic ovarian disease Chest - neuroge nic chest wall trauma, surgery, Chronic renal failure Cirrhosis Epileptic seizures

Figure 1: Causes of hyperprolactinemia(5)

Prolonged hypoestrogenism secondary to hyperprolactinemia causes osteopenia. Bone loss occurs secondary to hyperprolactinemia- mediated sex steroid attenuation. Spinal bone density is decreased by approximately 25% in women with hyperprolactinemia (10) and isnot necessarily restored with normalization of prolactin levels.

The patients can also present with neurological symptoms caused by mass effects of the pituitary tumor. Symptoms include headaches and visual loss such as bitemporal hemianopia , hypopituitarism, seizures, and cerebrospinal fluid rhinorrhea (11).

DIAGNOSTIC EVALUATION

The evaluation is aimed at excluding physiologic, pharmacological and other secondary causes of hyperprolactinemia. A detailed drug history should be obtained because many medications cause hyperprolactinemia* with prolactin levels of less than 100 ng/ml.

Normal serum prolactin levels vary between 5 and 25 ng/ml in females although physiological and diurnal variations do occur.[12] Serum prolactin levels are higher in the afternoon than 2in the morning, and hence should preferably be measured in the morning.

According to the Endocrine Society Guidelines for diagnosis and treatment of hyperprolactinemia(13), a single measurement of serum prolactin is recommended to establish the diagnosis of hyperprolactinemia; a level above the upper limit of normal confirms the diagnosis as long as the serum sample was obtained without excessive venipuncture stress(14).

Pitfalls in Lab diagnosis

Macroprolactinemia: The big prolactin or Macroprolactin is a less bio-active form consisting of dimers, trimers, or polymers of prolactin or prolactin-immunoglobulin immune complexes and it should be suspected when a patient's clinical history and/or radiological data are incompatible with the PRL value.(15,16) It is detected by polyethylene glycol precipitation method although gel filtration chromatography remains the gold standard.(17)

Hook Effect: When there is a discrepancy between a very large pituitary tumour and a mildly elevated prolactin level, serial dilution of serum samples to eliminate an artefact that can occur with some immune-radiometric assays due to saturation of the capture antibodies is recommended.(18)

Other Laboratory Studies

Serum TSH,blood urea nitrogen and creatinine should be done as hypothyroidism and renal failure are the two common causes of increased PRL.

Pregnancy should always be excluded unless the patient is postmenopausal or has had a hysterectomy. In addition, hyperprolactinemia is a normal finding in the postpartum period.

Role of Imaging

Any patient who has hyperprolactinemia without an identified cause requires imaging of the hypothalamic-pituitary area. A mildly elevated serum prolactin level may be due to a non-functioning pituitary adenoma or cranio-pharyngioma compressing the pituitary stalk,

although prolactin levels that are very high (>250 ng/mL) are almost always associated with a prolactinoma.[19] Magnetic resonance imaging (MRI) with gadolinium enhancement provides the best visualization of the sellar area.

MANAGEMENT

The treatment of hyperprolactinaemia depends on the underlying causes, natural course of the disease and the aim of treatment. The goals of treatment for are

- Normalization of prolactin level
- Restoration of gonadal function and fertility
- Avoidance of the adverse effects of chronic hyperprolactinemia like osteoporosis.

An additional goal of treatment in macroprolactinoma patients is tumour shrinkage with relief of mass symptoms. Current therapeutic options include medical therapy, surgery and radiotherapy.

Management of Drug induced Hyperprolactinemia

Although hyperprolactinemia commonly occurs with psychotropic medication use, only a minority of patients - typically those with hypogonadism need to be considered for treatment. After a work-up to rule out alternative causes of hyperprolactinemia, and bone density measurement, gonadal steroid replacement should be considered to preserve skeletal health and maintain compliance with a successful psychiatric medication regimen.The treating psychiatrist should be consulted for any change in psychotropic regimen.

Whether to treat a patient who has antipsychotic drug-3induced hyperprolactinemia with a dopamine agonist remains controversial. Some studies suggest that dopamine agonist therapy will normalize prolactin levels in only up to 75% of such patients but may lead to exacerbation of the underlying psychosis.(20-23)

Management of Idiopathic Hyperprolactinemia

In about 40% of moderate hyperprolactinemia, the cause of PRL hypersecretion cannot be determined. In such cases, it is classified as idiopathic hyperprolactinemia. Medication treatment with dopamine agonists is effective and cyclic menses are restored in 70-90% of the women within 6-8 weeks. Ovulatory cycles return in 50-75% of women (24) but treatment is required for at least one year depending on the response of the woman. As soon as pregnancy is confirmed, dopamine agonists should be immediately stopped.

Medical Therapy

Dopamine agonists have become the treatment of choice for the majority of patients with hyperprolactinemia namely bromocriptine and cabergoline. Bromocriptine was the first dopamine agonist to be introduced into clinical practice. It is a semisynthetic ergot derivative of ergoline, a D2 receptor agonist with antagonist properties at D1 receptors. Its half-life is relatively short and has to be taken 2 or 3 times daily.[25]It is effective in normalizing serum prolactin levels and restoring gonadal function in 80 to 90% of patients with varying degrees of tumor size reduction..[26] The most common adverse effects are nausea, vomiting and headache(up to 60% of patients). Postural hypotension is common especially when initiating therapy and can result in dizziness (25%). Other side effects include a Raynaud-type syndrome of painless digital vasospasm, drowsiness, fatigue, leg cramps, insomnia, blurred vision, and paresthesia.[27]

Side effects can usually be minimized by introducing the drug at a very low dosage (0.625 or 1.25 mg/d), taking the tablets with food and by very gradual dose escalation. Therapeutic dosages are generally in the range of 2.5 to 15 mg/d in hyperprolactinemic patients, but 5 to 17%[28]of patients are found to be resistant, requiring dose up to 30 mg/d. 26] Another alternative to oral treatment is vaginal usage of the same drug which is well tolerated. Vaginal absorption is nearly complete and first-pass metabolism via liver is avoided allowing lower therapeutic dosing.[29] It is also available in a long acting form (depot-bromocriptine) for intramuscular injection and a slow release oral form.[30,31]

Cabergoline is an ergoline derivative with high affinity and selectivity for the D2 receptor. It has an extremely long plasma half-life of about 65 hours allowing once- or twice-weekly administration. It has been shown to achieve normal serum prolactin levels in 85 to 86% and restoration of normal gonadal function in 90 to %.[32,33]

Cabergoline and bromocriptine have been compared in a multicenter collaborative study involving 459 women with hyperprolactinemic amenorrhea..[34] Stable normoprolactinemia was achieved in 186 of the 223 (83%) women in the cabergoline group compared with 138 of 236 (59%) women in the bromocriptine group (P <0.001).Resumption of ovulatory cycles or pregnancy occurred in 72 and 52% respectively (P <0.001).

Cabergoline is more effective and causes fewer adverse effects than bromocriptine. However, it is much more expensive and is often used in patients who cannot tolerate the adverse effects of bromocriptine or in those who do not respond to bromocriptine.

Therapy should be continued for approximately 12-24 months (depending on the degree of symptoms or tumor size) and then withdrawn if prolactin levels have returned to the normal range. After withdrawal, approximately one sixth of patients maintain normal prolactin levels. Response to therapy should be monitored by checking fasting serum prolactin levels and checking tumor size with MRI. Most women (approximately 90%) regain cyclic menstruation and achieve resolution of galactorrhea.

Management of Hyperprolactinemia- related Infertility

Inconstant ovulation and chronic anovulation are conditions observed in hyperprolactinemic patients as well as the occurrence of frequent luteal phase defects. In order to induce fertility it is important to maintain the effective PRL lowering dose for 10–12 months since it takes time to normalise ovulatory cycles and half of the pregnancies occur after the first six months of therapy. If ovulation does not occur despite the normalized PRL to increase the success rate a cyclical treatment with clomiphene citrate can be added.(35) In patients with idiopathic hyperprolactinemia after treatment with bromocriptine, in 80% women PRL levels are normalized, and in the absence of other causes of infertility, pregnancy occurs in 60-80%. (36)

Management of Pregnancy in women with hyperprolactinemia- unrelated to Prolactinoma

Dopamine agonists are the treatment of choice and women who are not harbouring any prolactinoma should stop dopamine agonist after confirmation of pregnancy. Routine prolactin monitoring should not be done.

Management of Prolactinoma

Cabergoline is considered to have higher efficacy in normalizing prolactin levels and pituitary tumor shrinkage. In a placebo-controlled study, cabergoline treatment (0.125–1.0 mg twice weekly) for 12–24 months in patients harboring prolactin-secreting microadenomas resulted in normalization of prolactin levels in 95% of patients. Cabergoline restored menses in 82% of women with amenorrhea.(37). I-n a retrospective study of 455 patients, cabergoline normalized prolactin levels in 92% of patients with idiopathic hyperprolactinemia or a microprolactinoma and in 77% of 181 patients with macroadenomas.(38) In pregnant women with prolactinoma bromocriptine is the treatment of choice due to its larger published data as no congenital malformation has been reported till now, and its shorter half life as compared to cabergoline.

When to discontinue therapy

Four recent studies (39–42) suggest that in a subset of patients, dopamine agonist withdrawal may be safely undertaken after two years in patients who have achieved normoprolactinemia and significant tumor volume reduction. The risk of recurrence after withdrawal ranges from 26 to 69%. All studies have shown that recurrence is predicted by prolactin levels at diagnosis and by the tumor size.

For patients who after two years of therapy have achieved normal prolactin levels and no visible tumor remnant and for whom dopamine agonists have been tapered or discontinued, follow-up includes: 1) measurement of serum prolactin levels every 3 months for the first year and then annually thereafter; and 2) MRI if prolactin increases above normal levels.In women with micro-prolactinomas, it may be possible -to discontinue dopaminergic therapy when menopause occurs.

Surgery

General indications for pituitary surgery include patient drug intolerance, tumors resistant to medical therapy, persistent visual-field defects in spite of medical treatment, and patients with large cystic or hemorrhagic tumors. Trans-nasal/trans-sphenoidal

microsurgical excision of prolactinoma is the procedure of choice. Hyperprolactinemia recurred within 5 years after surgery in about 50% of patients with microprolactinomas who were initially thought to be cured.(43) Re-evaluation of long-term results indicates a success rate of about 75% for surgical removal of micro-prolactinoma. However, the results of surgery for macro-prolactinoma are poor with a long-term success rate of only 26%.(44)

Radiotherapy should be reserved for resistant or malignant prolactinomas. Normalization of hyper-prolactinemia occurs in approximately one third of patients treated with radiation. Radiation therapy is associated with side effects including hypopituitarism and, rarely, cranial nerve damage or second tumor formation (45).

Conclusion:

Once diagnosis of hyperprolactinemia is confirmed the underlying cause of the disorder needs to be determined and common causes like hypothyroidism and drug intake should be ruled out. Medical therapy is the mainstay of treatment in most of the women with surgery being reserved for patients who are unresponsive to medical therapy. Cabergoline, which has a long half-life allowing once or twice weekly dosing, and a better tolerability profile, has become the dopamine agonist of choice. The management of pituitary adenomas requires a multidisciplinary approach.

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5 Amenorrhea in Polycystic Ovary Syndrome (PCOS)

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PCOS is the most common gynecologic endocrine disorder represented by a cluster of signs and symptoms. It is the most common cause of anovulation, which may lead to oligomenorrhea, amenorrhea , and abnormal uterine bleeding. Chronic anovulation increases the risks of endometrial hyperplasia and cancer due to unopposed estrogen dominance.

The diagnostic criteria are many, yet controversial. The most commonly followed Rotterdam Criteria established in 2003 conclude that the disorder is diagnosed if two of the following three criteria are present [1]:

1. Oligoanovulation
2. Clinical or biochemical signs of hyperandrogenism
3. Polycystic appearing ovary(ies) on ultrasonography with a volume of ≥ 10 ml, and /or more than 12 follicles of sizes between 2 and 9 mm

Pathogenesis of Oligo/amenorrhea

The absence of menses in a girl / women of reproductive age is related to the disturbance of normal hormonal and physiological mechanisms.

Normal Ovulation Cycle

The normal physiological mechanism of ovulation requires perfect coordination between the hypothalamus, pituitary, ovary and the uterus at all levels. Towards the end of a menstrual cycle, the corpus luteum regresses and ovarian hormones estradiol, progesterone and inhibin-A plummet to basal levels. This sudden crash of hormones withdraws the negative feedback on the hypothalamus and the pituitary. Pulse frequency of gonadotropin-releasing hormone (GnRH) secretion increases and stimulates the pituitary secretion of follicle-stimulating hormone (FSH). FSH acts on ovaries to recruit a fresh cohort of follicles. Serum Inhibin B and estrogen levels rise starting from early follicular phase. During the mid-follicular phase, FSH-stimulated aromatase activity in the granulosa cells helps in the continued follicular development and estrogen secretion. Estrogen and inhibin A levels steadily increase and lead to increase in Luteinizing Hormone (LH) pulse frequency. FSH levels gradually decline but remain adequate enough to support the dominant follicular growth. The rest of the follicles undergo apoptosis. During the later part of follicular growth, estrogen and FSH lead to increased LH receptors in the dominant follicle. After exceeding the threshold concentration, estradiol induces the mid-cycle LH surge, which completes follicular maturation, ovulation and formation of corpus luteum. Serum estradiol levels fall precipitously post-ovulation and the corpus luteum starts secreting progesterone. Under the effect of progesterone, the endometrium transforms from proliferative to secretory morphology. If there is no pregnancy, corpus luteum regresses and the hormonal support to endometrium is withdrawn, which eventually leads to menses. Any defect at any level of this normal physiology of female can cause anovulation / amenorrhea [2].

PCOS and Gonadotropin Secretion

Women with PCOS have an increased serum LH concentration, low-normal FSH levels, and consequent increased LH to FSH ratios [3-5]. LH pulse frequency contributes to increased LH levels [6]. LH pulse frequency in PCOS is relatively constant at one pulse per hour and lacks the normal cyclic variation. This hourly LH pulse frequency is within the range of frequencies observed in the late follicular phase of normal women. Increased LH frequency may be an intrinsic defect in hypothalamic function. An increase in GnRH pulse frequency, the negative feedback effects of chronically elevated estrone levels from peripheral conversion of androstenedione to estrone and normal to mildly increased inhibin B levels all contribute to low FSH levels [7,8]. Excessive LH secretion leads to disordered folliculogenesis and anovulation, leading to oligo/amenorrhea [9,10].

Normal ovulation causes normal menses that is cyclical at 21-35 days' interval. Intermenstrual

intervals of lesser than 21 and more than 35 days are indicative of ovulatory dysfunction[11]. Menstrual dysfunction in the form of oligo/amenorrhea is observed in 60-85% of women with PCOS, and as polymenorrhea in less than 2% [12,13]. Anovulation in PCOS results in amenorrhea and oligomenorrhea [14]

Management

Chronic anovulation in PCOS leads to oligomenorrhea (with less than eight menstrual cycles annually) which may be the presenting symptom in many such women. Some also present with amenorrhea or abnormal uterine bleeding. Due to constant, unopposed estrogen exposure, endometrial abnormalities in the form of endometrial hyperplasia and even cancer are more common in such women [15, 16]. Chronic anovulation, hyperinsulinemia and obesity all contribute to developing endometrial cancer in women with PCOS [17,18]. Endometrial sampling must be done for risk assessment for endometrial abnormalities taking into account the age, endometrial thickness, number of cycles per year, degree of obesity and hyperinsulinemia and hyperandrogenic milieu. An endometrial thickness exceeding 12 mm is suggestive of endometrial hyperplasia and may warrant a sampling [19].

The most commonly prescribed treatment for menstrual abnormalities in PCOS is the combined oral contraceptive (COC) pill. It provides endometrial protection through its progesterone and thus stunts endometrial growth from unopposed estrogen and cycles regularise with lighter bleeding. Besides, COCs are effective for suppressing LH-mediated ovarian androgenesis, thus correcting the hyperandrogenic milieu [20-22]. Estrogen is contraindicated in some women, in them progesterone-alone preparations can be used either in a continuous or a cyclical form.

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6 Developmental Anomalies Causing Amenorrhoea

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Dr Megha Jayaprakash

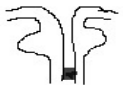
Around 7 % of young females present with a reproductive tract anomaly. A clear knowledge of the steps of development of the uterus, cervix and vagina from the Mullerian (Paramesonephric) ducts is important to understand the classification of Mullerian anomalies. The steps are summarised in brief below.

After the 5 th week of IUL, two Mullerian ducts grow towards each other in the midline.Fusion of the lateral portions of these ducts start to occur in a caudocranial direction from 7-8 wks of IUL and is completed by 12 weeks of IUL with formation of a uterovaginal canal. Fusion results in the formation of a midline septum which gets resorbed from below upwards and resorption is completed by 20 weeks of IUL..Concavity of the fundus of the uterus changes to domeshaped. The fallopian tubes,uterus,cervix and upper part of vagina including the fornices are of Mullerian origin.

Recent studies hold that the vagina develops under the influence of the müllerian ducts and estrogenic stimulation.A solid vaginal cord from the lower end of the fused uterovaginal canal elongates and vertically fuses with the sinovaginal bulbs from the(endodermal) urogenital sinus by 8 weeks IUL.This results in a vaginal plate formation. Most of the vagina is formed by the canalization of the vaginal plate between 20-26 weeks IUL.

Though there are some doubts regarding the extent of vagina that develops from the Mullerian ducts and whether the vagina remains open in fetal life,it is agreed that the vagina has a dual origin.The hymen is the septum at the junction of the sinovaginal bulbs and the urogenital sinus proper.

Hence Mullerian anomalies can be defects in any one or more of the following:
1) Synthesis 2) Fusion 3) Resorption

Disorder o	Condition	Terminology	Diagram	Structures +/
Synthesis	Both Mullerian ducts absent	Mullerian Agenesi MRKH Syndrome		Both Fallopian tubes m be + Lower part of vagina +
Synthesis	One side Mullerian duct absent	Unicornuate uteru		One Fallopian tube + Half of uterus,cervix an upper vagina +
Lateral fusion	Both Mullerian ducts form but fail to fuse	Didelphic uterus		2 tubes 2 uteri 2cervix 2upper vagina
Lateral fusion	Both ducts present but incomplete fusion	Bicornuate unicollis,bicornua bicollis		2 tubes 2 uteri 1 vagina
Resorption	Both ducts present and fuse,but septum fails to resorb	Septate,Subsepta uterus		Midline septum presen
Resorption	Fundus does not become domeshaped	Arcuate uterus		Flat topped fundus or concave

One of the oldest and most familiar classification systems for developmental abnormalities of Mullerian ducts is the one by American Fertility Society (AFS) Buttram and Gibbons in 1988(Table 1)

CLASS	ANOMALY
I	Segmental Mullerian Agenesis/hypoplasia A Vaginal B Cervical C Fundal D Tubal E Combined
II	Unicornuate A Communicating rudimentary horn B Noncommunicating horn C No uterine cavity D No horn
III	Didelphis
IV	Bicornuate A Complete B Partial
V	Septate A Complete B Partial
VI	Arcuate
VII	Diethylstilbesterol - related

It has an embryological basis and focuses mainly on lateral fusion defects of the uterus. A more detailed embryological classification that incorporates vertical fusion defects and unusual configurations is the one given below.

Modified American Fertility Society Classification of Uterovaginal Anomalies

Class I. Dysgenesis of the Müllerian ducts
Class II. Disorders of vertical fusion of the Müllerian ducts
A. Transverse vaginal septum
1. Obstructed
2. Unobstructed
B. Cervical agenesis or dysgenesis
Class III. Disorders of lateral fusion of the Müllerian ducts
A. Asymmetric-obstructed disorder of uterus or vagina usually associated with ipsilateral renal agenesis
1. Unicornuate uterus with a noncommunicating rudimentary anlage or horn
2. Unilateral obstruction of a cavity of a double uterus
3. Unilateral vaginal obstruction associated with double uterus
B. Symmetric-unobstructed
1. Didelphic uterus
a. Complete longitudinal vaginal septum
b. Partial longitudinal vaginal septum
c. No longitudinal vaginal septum
2. Septate uterus
a. Complete
1) Complete longitudinal vaginal septum
2) Partial longitudinal vaginal septum
3) No longitudinal vaginal septum
b. Partial
1) Complete longitudinal vaginal septum
2) Partial longitudinal vaginal septum
3) No longitudinal vaginal septum
3. Bicornuate uterus
a. Complete
1) Complete longitudinal vaginal septum
2) Partial longitudinal vaginal septum
3) No longitudinal vaginal septum

b. Partial
1) Complete longitudinal vaginal septum
2) Partial longitudinal vaginal septum
3) No longitudinal vaginal septum
4. T-shaped uterine cavity (diethylstilbestrol related)
5. Unicornuate uterus
a. With a rudimentary horn
1) With endometrial cavity
a) Communicating
b) Noncommunicating
2) Without endometrial cavity
2) Without endometrial cavity
b. Without a rudimentary horn

Class IV. Unusual configurations of vertical-lateral fusion defects

ESHRE/ESGE CONUTA classification that was proposed in 2013 by Grimbizis et al allows a more precise anatomical description of any defect or combination of defects in the uterus,cervix and vagina.It also has a place for unclassified malformations.

UTERINE Anomaly

Main class	Subclass
U0 Normal uterus	
U1 Dysmorphic uterus	a Tshaped b Infantile c others
U2 Septate uterus	a Partial b Complete
U3 Bicorporeal uterus	a Partial b Complete c Bicorporeal Septate
U4 Hemi uterus	a with rudimentary cavity b without rudimentary cavity
U5 Aplastic	a with rudimentary cavity b without rudimentary cavity
U6 Unclassified Malformations	

CERVICAL/VAGINAL Anomaly

Co -Existent Class	
C0	Normal Cervix
C1	Septate Cervix
C2	Double "Normal" cervix
C3	Unilateral cervical aplasia
C4	Cervical aplasia
V0	Normal vagina
V1	Longitudinal non -obstructing vaginal septum
V2	Longitudinal obstructing vaginal septum

It is evident that AFS Class I and Classes I and II of Modified AFS classification as well as Classes U5 C4 V3 and V4 of ESHRE classification are obstructive anomalies that can present with amenorrhoea early in reproductive life.

This chapter will focus on the Mullerian anomalies that present with primary amenorrhoea.

IMPERFORATE HYMEN

It comes in Class V3 of ESHRE/ESGE classification.

This occurs when the hymen which is formed by invagination of the posterior wall of the urogenital sinus does not undergo spontaneous dissolution during the perinatal period.It is generally a sporadic anatomical defect and is usually isolated.But there are case reports of familial occurrence and association with Mullerian anomalies.

As the HPO axis is intact and the uterine endometrium is responsive to cyclic ovarian hormones,there is cyclic shedding of the menstrual endometrium. This results in the collection of blood in the vagina(haematocolpos) and in the uterine cavity(haematometra).At the time of expected menarche,these patients develop cyclical abdominal and pelvic pain due to the obstructed blood flow/Cryptomenorrhoea.They may also present with urinary retention due to the pressure of the distended vagina pressing on the urethra .

Classical presentation is as primary amenorrhoea with well developed secondary sexual characteristics. Examination reveals the vaginal orifice closed by a bulging (often bluish) thin membrane which becomes prominent with a Valsalva maneuver.(Fig 1A)

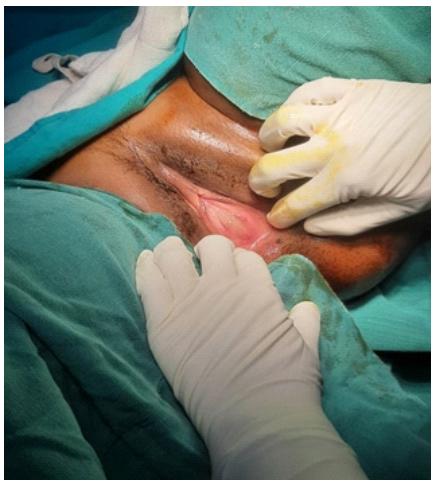


Figure 1A Before surgery

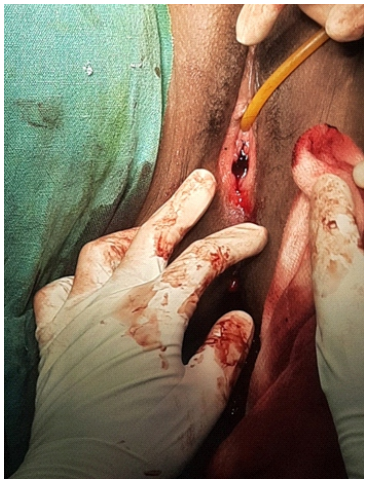
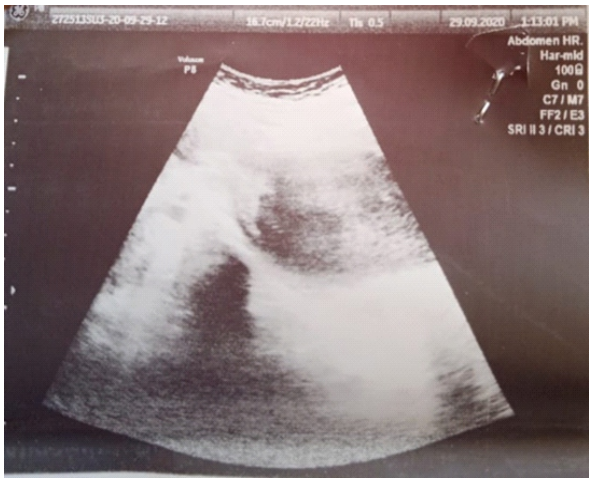


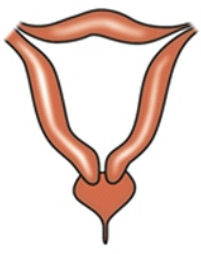
Fig 1B After surgery



Ultrasound scan usually picks up the haematocolpos (Fig 1C) and haematometra if present.

Definitive treatment is in the form of surgery which should not be delayed as there is risk of endometriosis and permanent inflammatory scarring.The classical procedure is putting a cruciate incision on the bulging membrane to let the collected blood out(Fig 1B) and oversewing the hymenal edges after giving a single dose of prophylactic antibiotics.An alternative method is to do a sterile puncture and widen it to about 0.5 cm to insert a Foley's catheter for irrigation of vagina with saline.This catheter can be left in place for another 2 weeks for complete drainage.

LOWER VAGINAL ATRESIA



Partial vaginal atresia

Fig 2: Courtesy-Prof Presannakumari Bhanumathy(Retd) Dept of OBG Govt Medical College Trivandrum)

This belongs to Class I in AFS classification and occurs when the müllerian portion of the vagina fails to canalize with the urogenital sinus portion of the vagina. Patients have age appropriate secondary sexual characteristics and will present with cyclic pelvic pain and amenorrhoea at puberty just like patients with imperforate hymen.

A vaginal dimple is present on examination, however the bluish hue is not seen.A rectal examination may be done to determine the level of obstruction but MRI of pelvis should be done to determine the distance between the lower end of the haematocolpos and the perineum.This distance is important in deciding the management. When the distance of the atretic vagina is ≤3 cm from the perineum, a straightforward vaginal pull-through procedure may be performed . When the distance is more than 3 cm, use of a graft becomes necessary to minimize risk of vaginal stricture postoperatively.

CERVICAL ATRESIA / DYSGENESIS

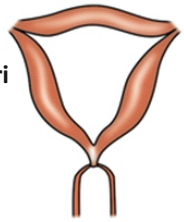


**Fig 3: Courtesy-Prof Presannakumari Bhanumathy(Retd)
Dept of OBG Govt
Medical College Trivandrum)**

Cervical atresia is relatively rare and is a AFS Class I (ESHRE C4)anomaly.When present, it is usually seen in association with absence or atresia of a portion or whole of the vagina .As the small uterine cavity fills up quickly,the patient presents soon, usually after 1 - 2 menstrual cycles with pelvic pain and amenorrhoea.In the absence of the cervical support,the distended uterus has a tendency to undergo torsion and present as acute abdomen.

On examination,there is usually a vaginal dimple with no bulge.Examination under anaesthesia along with Ultrasound scan and MRI will be needed to help in preoperative diagnosis which is still challenging.It is often difficult to accurately diagnose as the lowermost part of the uterus may be ballooned out to mimic an upper vagina versus a truncated cervix.

Preoperative planning and surgical management options vary depending on whether the cervix is totally absent or is dysgenetic and counseling regarding the options will depend on the diagnosis.

If the cervix is totally absent, it is difficult to construct a neocervix. Creation of the unique mucus producing endocervical mucosa which is important in fertility, is next to impossible.One option is to bridge the lower end of the uterus to the vagina after excising the atretic portions similar to posttrachelectomy and then opt for IVF. But this procedure has significant morbidity in the form of retrograde menstruation,endometriosis,sepsis and strictures requiring reoperations There are reports of experimental methods to keep the tract patent using silicone stents and creation of a neocervical lining with intestinal grafts but these are based at anecdotes.

If the patient is unwilling for this approach, Laparoscopic removal of the uterus after ureteral stenting along with vaginoplasty in the same sitting can be offered, which will protect the ovaries from damage by endometriosis.Such a patient can then opt for IVF and surrogacy.

In case of cervical dysgenesis, various forms are noted.
a) fragmented parts with no connection to uterus
b) hypoplastic cervix with no endocervical lumen
c) cervical body replaced by a fibrous band with or without endocervical glands
d) well formed cervical body but a portion of the lumen is obliterated
Fragmented cervix usually warrants hysterectomy. In cases where some amount of stroma and endocevical glands are present,Cannulization techniques to create a cervicovaginal anastamosis are described.Endocervical grafting procedures for cervical fibrous band are also reported.But morbidity of these procedures is quite high with low success rates.

TRANSVERSE VAGINAL SEPTUM

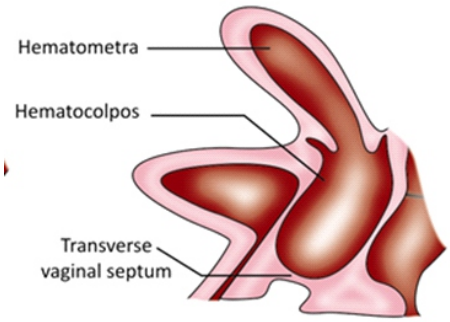


**Fig 4: Courtesy-Prof Presannakumari Bhanumathy(Retd)
Dept of OBG Govt Medical College Trivandrum)**

It is a modified AFS Class IIA and ESHRE class V3 defect.This is considered a vertical fusion defect as the vaginal plate fails to canalize during embryogenesis.It is considered a maldevelopment of the urogenital sinus as it fails to fuse with the mullerian structures.This is much rarer than vaginal or uterovaginal agenesis.Often quoted incidence rate is around 1 in 72,000.

In contrast to other Mullerian anomalies,transverse vaginal septum is not commonly associated with other anomalies.Imperforate anus and bicornuate uterus may be seen occasionally.The most common site for a transverse vaginal septum is the upper vagina(46%),followed by midvagina(40%) and lower vagina(14%).The septum tends to be thicker as it gets closer to the cervix.

Neonates and young infants can sometimes present with lifethreatening complications due to fluid retention.The endocervical and upper vaginal secretions in response to maternal oestrogens can cause hydrocolpos and fluid retention above the septum.It can produce hydroureteronephrosis, Inferior venacaval compression, constipation, intestinal obstruction and cardiorespiratory failure due to obstruction to diaphragmatic movements.

But the classical picture is a pubertal girl with age appropriate secondary sexual characteristics presenting with primary amenorrhoea and cyclical abdominal pain.On examination, there may be a shortened vagina varying in length with the site of the septum,no cervix visible and no bulging on Valsalva maneuver.A haematocolpos may be palpable above the septum on doing a rectal examination.If the septum is not identified and excised early on,severe endometriosis can develop and a fixed mass may be palpable on bimanual pelvic examination due to formation of haematometra and haematosalpinges. But sometimes there may be a tiny orifice through which the patient menstruates as seen in Figure 5

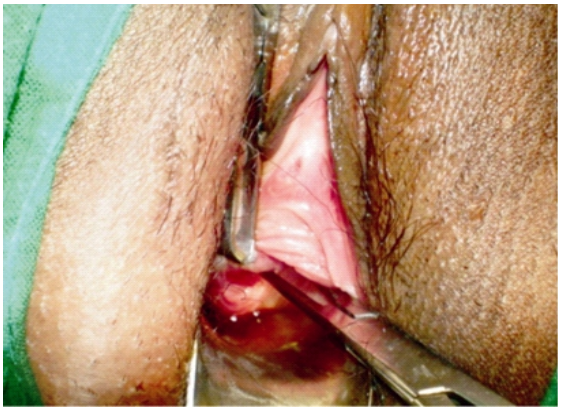


Fig 5: Courtesy-Prof Presannakumari Bhanumathy(Retd) Dept of OBG Govt Medical College Trivandrum)

Ultrasound pelvis can reveal haematocolpos,haematometra and haematosalpinges.but an MRI is essential to delineate the level and thickness of the septum (atretic portion of the vagina) and for preoperative planning. Excision of transverse vaginal septum should be done by trained specialists.

A transverse incision is made through the vault of the short vagina and the areolar tissue between the bladder and rectum is carefully dissected to reach the cervix.The edges of the upper and the lower vaginal mucosa are undermined and mobilized to anastomose with interrupted delayed absorbable sutures.

For high and thick(more than 1 cm) septae, various methods are described.One is to use Z-plasty, Y-plasty, or cross-plasty technique to reduce the thickness of the septum.If the atretic vaginal segment is too long to bridge, use of grafts will become necessary. Sometimes the thick septum appears thinned out in MRI due to pressure of the haematocolpos.Hence the surgeon should be prepared to use these methods if the need arises.

It is important to maintain patency and avoid strictures by keeping a soft foam rubber mould covered in sterile condom inside the vagina for atleast 4-6 weeks.Healing can be evaluated after 10 days. In a girl who is not sexually active,its advised to wear lubricated dilators/silicone mould for many months during the constrictive phase of healing to maintain length and patency.

UTEROVAGINAL AGENESIS (MAYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME)
It belongs to Class Ie in AFS/ASRM classification and Class U5 C4 V4 in ESHRE/ESGO classification.

Mullerian agenesis is the second most common cause(10-15%) for Primary amenorrhoea and occurs one in 5000 newborn girls.It is characterized by vaginal agenesis with varying degrees of uterine agenesis.

Most cases are sporadic but a few familial aggregates have been identified. An association with errors in fetal or maternal galactose metabolism(galactose-1-phosphate Uridyltransferase GALT gene mutations) resulting in increased intrauterine galactose exposure and mullerian anomaly has been noted.There are also isolated reports of HOX ,WNT4 and HNF1B gene mutations but exact causative factor is still unknown.

Though MRKH syndrome is characterized by absent or rudimentary uterus with vaginal agenesis, 7—10 % of them can have functioning endometrium. The ovaries are entirely normal in the great majority of these patients as the karyoptype is normal female 46,XX.

Due to the close embryological association between Mullerian(paramesonephric) and Wolffian (mesonephric) ducts, 15-40% of MRKH syndrome has urological anomalies like unilateral renal agenesis, ectopic and horse shoe kidney as well as duplex collecting system.

Classification of MRKH Syndrome

Type A(typical)(64%)-isolated symmetrical uterovaginal aplasia / hypoplasia

Type B(atypical)(24%)-asymmetrical UV aplasia/hypoplasia with malformations of tubes, ovaries +/- renal system

Type C (MURCS) (12%)-Mullerian duct aplasia,renal dysplasia,cervicothoracic somite anomalies(heart and skeletal)-may be familial(WNT4 gene mutations)

Typical presentation is a pubertal age girl of normal stature with well developed secondary sexual characterisitics presenting with primary amenorrhoea. Unlike transverse blockage of the mullerian system as in imperforate hymen and transverse vaginal septum, cyclic pain is usually absent in Mullerian agenesis unless functioning endometrium is present. On examination there will be a vaginal dimple or 1-2 cm blind ending vaginal pouch with otherwise normal external female genitalia.(Fig 6).This is the part of the vagina that develops from the urogenital sinus.

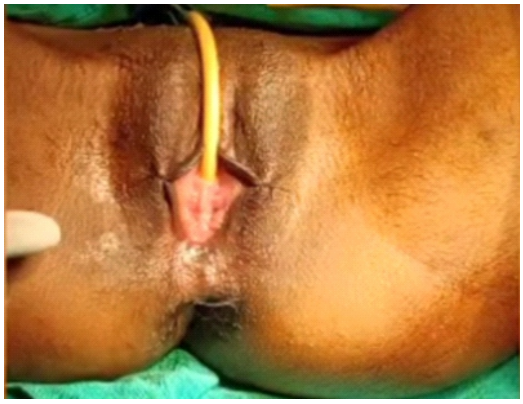


Fig 6

The diagnosis of MRKH can be arrived at with history and examination but karyotyping is justified to rule out Complete Androgen Insensitivity Syndrome (46,XY) which can present in a similar fashion. Male sex hormones in MRKH are in the normal female range. Absence of uterus with presence of ovaries can be made out with an ultrasound scan but MRI is more accurate to delineate finer details as well as pick up urological anomalies. MRI in Fig 7 shows uterine agenesis in a patient with MRKH syndrome

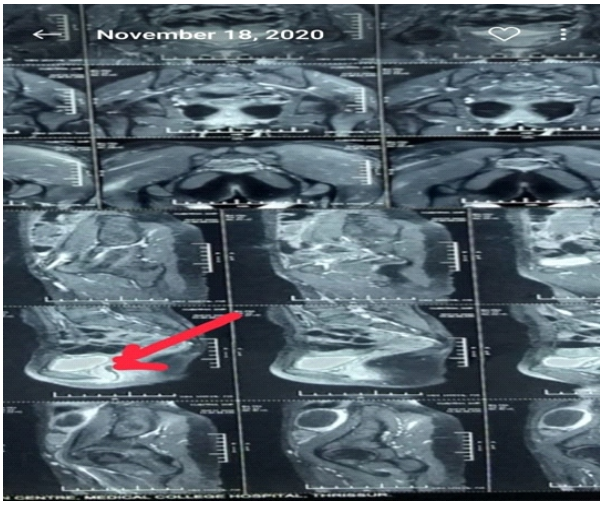


Fig 7

Empathetic counseling of the patient and family regarding the condition and the treatment options is of paramount importance. Management is essentially aimed at achieving a fair length of vagina for coital function. If there is the rare functioning endometrium,then laparaoscopic removal of the uterine remnant should be done.

She should be assured that vaginoplasty gives good results when done by trained specialists.She and her partner can have their genetic offspring by IVF with their own gametes and surrogate uterus.There is also the option of uterine transplantation that has evolved tremendously over the past decade.

Methods to create a neovagina may be classified into

1) Nonsurgical --Frank's dilators(active)
   -- Ingrams method(passive)
2) Surgical – Abbe-Wharton-McIndoe vaginoplasty
   – Williams vulvovaginoplasty
   – Colovaginoplasty/Ruge procedure
   – Davydov vaginoplasty
   – Makinoda's 2 step operation
   – Vecchietti operation

Frank's dilation

Active non surgical method of creating an artificial vagina using dilators made of different polymers. This was described in 1938 and ACOG still recommends this as the first line management to be

Ingram Technique

This is a passive method of dilation where the patient is instructed to sit on a dilator fitted to a specially designed bicycle seat every day for atleast 2 hours, The diameter of the dilator is increased on an average every month. Patient may be allowed to have coitus after the use of the largest dilator for 1 or 2 months. Otherwise continued dilation is required .If dilatation is unsuccessful or unacceptable, operative vaginoplasty is indicated

Abbe-Wharton-McIndoe operation

Most experts recommend this as the gold standard technique for vaginoplasty. The principles to be followed are

(a)dissection of an adequate space between the rectum and the bladder (b)Inlay split-thickness skin grafting and © cardinal principle of continuous dilatation during the contractile phase of healing

After inserting an indwelling urethral catheter and a finger in the rectum, a transverse incision is made on the mucosa of the vaginal vestibule(Fig 8) and dissection of the space between the bladder and rectum carefully until the undersurface of the peritoneum is reached. This creates the neovaginal space.

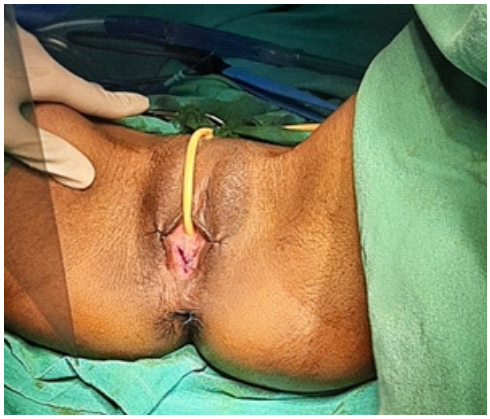


Fig 8

A split-skin graft that is uniformly thick and adequately long and wide is taken.(Fig 9)

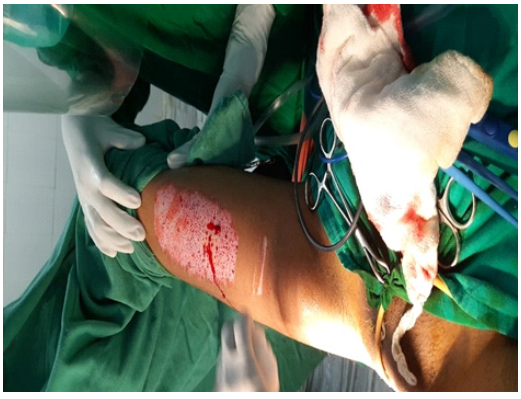


Fig 9

The Counseller-Flor modification of the McIndoe technique uses a sterilised foam rubber mold shaped for the vaginal cavity from a foam rubber block and covered with a condom (Fig 10)

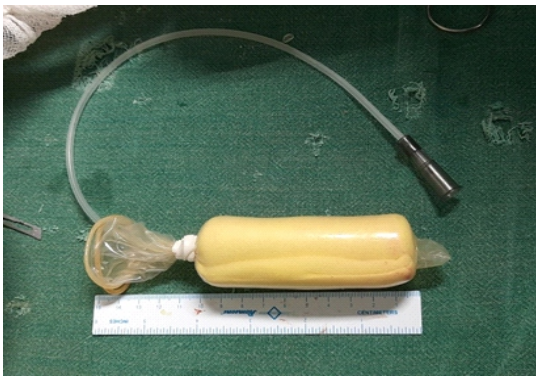


Fig 10

The skin graft is then placed over the form and its undersurface exteriorized and sewn over the form with interrupted vertical mattress sutures.(Fig 11)

Fig 11

The edges of the graft are sutured to the skin edge with absorbable sutures.

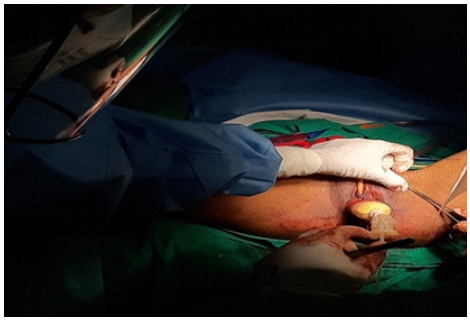
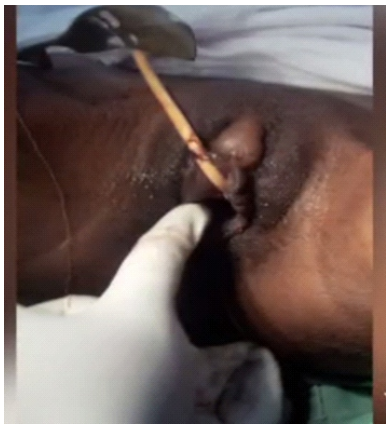


Fig 12

After 10 days, the form is removed and the neovagina is irrigated and checked. **(Fig 13)**



She is instructed to remove and clean the form daily and wear it continuously for 6 weeks. She can switch to wearing the mould at bedtime later.

Success rates in recent times is 80-100 %.Apart from bleeding, infection, constriction due to granulation tissue and graft failure,there is a 4 % postoperative fistula rate and enterocoele formation.

Buccal mucosa is being increasingly used as it has tissue similarities compared to native vagina with excellent healing and no visible scar.There are also exciting reports of the use of autologous in vitro grown vaginal tissue.

Williams vulvovaginoplasty

A horse-shoe incision is made in the vulva and skin is mobilized to form the perineal pouch /neovagina.It is technically simple with lesser complications and postoperative pain.There is no need for dilatation and it can be done in patients who do not intend to have intercourse in the near future.It is not applicable for patients with poorly developed labia and it creates an unusually angled vagina. It is considered the operation of choice for patients needing a reoperation due to failure of primary surgery and also it is useful in patients with pelvic kidney.

Colovaginoplasty/ Ruge procedure

It involves formation of a neovagina using sigmoid colon grafts.Advantage is ample vaginal length(12 cm) without vaginal dilatation and can be chosen where there is no other option of graft..Disadvantage is the need for laparotomy,mucus discharge from the neovagina.Ota and colleagues have reported a series done laparoscopically.

Davydov procedure

This technique uses peritoneum to line the neovagina.It involves dissection to create the neovaginal space, freeing up peritoneum from the pelvis,and sewing the apex closed from the abdominal side.This is done by a combination of vaginal and laparoscopic approaches.It requires postoperative long term use of dilators.

Makinoda's two step technique

It is a nongrafting method of vaginal creation.The initial step is noninvasive dilatation using a vaginal mold. In the second step ,the apex of the dilated vaginal space is incised and dissection between the bladder and rectum is carried to the peritoneal cavity. After peritoneal perforation, the uterine structures, when present, is pulled down and sutured to the newly created vaginal space. This also requires the long term use of postoperative moulds.

Vecchietti operation

The operative phase involves positioning an acrylic shaped olive at the perineum and the traction sutures extraperitoneally. The traction device, which provides constant traction on the perineal olive, is positioned on the abdomen. During the postoperative invagination phase, the neovagina is created by applying constant traction to the olive. The process reportedly occurs at a rate of 1.0 to 1.5 cm per day, developing a 10- to 12-cm vagina in 7 to 9 days.

Laparoscopic modification of Vecchietti operation is now popular.

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7 Amenorrhoea and Gonadal dysgenesis

Dr. Mandakini Pradhan

Definition:
Amenorrhoea refers to the absence of menstrual periods. It is subcategorised into primary and secondary causes.

Primary – failure to commence menses (absence of menarche) in girls aged 16+, in the presence of secondary sexual characteristics such as pubic hair growth and breast development, or girls aged 14+, in the absence of secondary sexual characteristics.

Secondary – cessation of periods for more than six months after the menarche (after excluding pregnancy).

Causes of amenorrhoea:
Outflow tract abnormality:
Congenital:
Mullerian agenesis
Imperforated hymen, Transverse vaginal septum
Complete androgen resistance
Acquired:
Asherman syndrome (intrauterine synechiae)
Cervical stenosis

Primary ovarian insufficiency
Congenital
- Turner syndrome or variant
- 46,XY gonadal dysgenesis

Receptor abnormalities and enzyme deficiency
- Complete androgen insensitivity syndrome
- 5-alpha reductase deficiency
- 17- alpha hydroxylase deficiency
- P450 oxidoreductase deficiency
- Estrogen resistance

Acquired
- Autoimmune destruction
- Chemotherapy or radiation

Pituitary
- Hyperprolactinemia

Empty sella syndrome
Autoimmune, Cushings syndrome
Infiltrative disease (e.s. Sarcoidosis)
Cocaine

Medications: like Antidepressants, Antihistamines, Antipsychotic, Opioids
Gonadotropin deficiency (e.g., Kallmann syndrome)
Traumatic brain injury
Eating disorder including celiac disease
Infection (e.g., meningitis, tuberculosis, syphilis)
PCOS
Endocrine disorder including thyroid dysfunction

Gonadal dysgenesis and amenorrhoea:
Gonadal dysgenesis is the name given to any of a multitude of conditions that can cause impaired development of the gonads, i.e., the testes or ovaries. The most notable of these conditions is Turner syndrome, a disorder affecting 1 in every 2500 live female births.

Understanding the genetics behind gonadal dysgenesis allows clinicians to better predict the disorder's phenotypic presentation, in turn, improving both screening methods for associated medical problems and the ongoing care of those medical problems.

Gonadal dysgenesis is a genetic condition due to errors in cell division and or alterations in genetic material, leading to complete or partial loss of gonadal development. The development of gonadal dysgenesis begins early either at fertilization or shortly after in the early stages of the embryo and fetus.

The causes of gonadal dysgenesis and amenorrhoea could be pure gonadal dysgenesis (46, XY female), Complete Gonadal Dysgenesis (46, XX) or Sweyer syndrome and Turner syndrome.

Pure Gonadal Dysgenesis

Pure gonadal dysgenesis is the term given to phenotypically female individuals with streak gonads who are of normal stature and have none of the physical stigmata associated with Turner's syndrome. Such individuals have either a 46,XX or 46,XY karyotype. The 46,XX defect may be inherited as an autosomal recessive, with 10% having associated nerve deafness. The 46,XY defect may be inherited as an X-linked recessive, with clitorimegaly occurring in 10 to 15% and gonadal tumors (gonadoblastoma) developing in 25% if the gonads are not removed

46,XY Gonadal Dysgenesis

Patients with pure gonadal dysgenesis are born as phenotypic females. Amniocentesis with a 46,XY karyotype that does not produce the expected phenotype on fetal ultrasonography now allows earlier diagnosis than was previously possible. Dorsal pedal edema and some Turner characteristics may be the only obvious somatic manifestations of the defect. Müllerian structures are present, but gonads are not palpable due to failure of gonadal differentiation. Testosterone and MIS are undetectable, indicating dysgenesis of the gonad.

Pure gonadal dysgenesis in XY females also occurs in individuals with *SOX9* mutations (campomelic dysplasia), with WT mutations (Denys–Drash syndrome), with duplications of the Xp21 region (*DSS* gene), and with deletions of the short arm of chromosome 9 (including the DMRT1 gene) and the long arm of chromosome 10. The gene locus involved in the last condition has not yet been identified. In all these genetic aberrations, additional clinical features of varying severity are associated, usually leading to substantial handicap. Investigation of XY females for the underlying genetic defect has been largely responsible for our present understanding of the genetic pathway in mammalian sex differentiation. As the underlying defect has been identified in only a proportion of XY females, other loci important in sex differentiation remain to be discovered.

Apart from pure gonadal dysgenesis, several other disorders are associated with sex reversal in XY females are as follows:

1. Androgen insensitivity (testicular feminization). This condition is the result of mutations of the X-linked androgen receptor gene. The developing testis secretes normal amounts of testosterone but the tissues are unable to respond due to the absence of androgen receptors. Affected individuals have normal female gender, are within the stature range of males, and develop breasts at puberty. However, they fail to menstruate, and pubic and axillary hair is scant. This is often the first indication of the condition. Sometimes, patients present with an inguinal hernia in childhood, and this leads to the discovery of testes in the inguinal canals; however, the testes usually remain within the pelvis and are only identified by laparotomy. This reveals a short, blind-ending vagina, the absence of uterus and fallopian tubes, and the failure of development of Wolffian structures. As there is a risk that testicular tumors (dysgerminoma) may develop, the testes are removed and the patient maintained for life on a small daily dose of estrogen. The disorder is inherited as an X-linked recessive trait and the carrier state in normal females may sometimes be recognized by the patchy distribution of sex hair. Half the XY offspring of a carrier are at risk of being affected. Incomplete forms of androgen insensitivity are also recognized, due to mutations of the androgen receptor locus distinct from the complete form. Partial masculinization occurs leading to sexual ambiguity at birth and virilization at puberty.

2. 5-α-Reductase deficiency (pseudovaginal perineoscrotal hypospadias). Deficiency of 5-α-reductase leads to failure of conversion of testosterone to dihydrotestosterone. XY infants with severe enzyme deficiency have a small hypospadic phallus, a blind vaginal pouch, and absent Müllerian derivatives. Over 50% are raised as XY females. At puberty, the patients virilize, do not develop breasts, and undergo a gender identity change to male gender.

3. Several other rare disorders of steroid biosynthesis may lead to sex reversal in XY females:
(a) testicular unresponsiveness to gonadotrophin;
(b) congenital lipoid adrenal hyperplasia;
(c) 3-β-hydroxysteroid dehydrogenase deficiency;
(d) 17-hydroxylase deficiency; and
(e) 17 β-hydroxysteroid oxidoreductase deficiency.

Deficiency of each of these enzymes can be associated with female external genitalia, absence of Müllerian derivatives, and a blind vaginal pouch.

46, XX Gonadal Dysgenesis

Patients with pure gonadal dysgenesis and 46,XX karyotype have a normal stature, sexual infantilism, and bilateral streak gonads. A marked heterogeneity, both genetically and clinically, has been noted in the expression of the disease, even in the same kindred. The molecular basis of the condition is still not well understood. The frequency of consanguinity in affected families points to an autosomal gene necessary for normal ovarian development and function. Alternatively, the condition may result from an X-linked gene mutation or deletion in sporadic cases. Adult height is lower in 46,XX than in 46,XY gonadal dysgenesis, which suggests the existence of a Y-specific growth gene that promotes height independently of gonadal steroids. The main clinical features are the lack of stigmata of Turner syndrome. Presenting signs at the age of puberty include lack of breast development, primary amenorrhea, and elevated gonadotropins.

Pure 46, XX gonadal dysgenesis is typically caused by alterations to genetic information needed for ovarian development, present at the proximal Xp, and distal Xq regions of the X chromosome. These alterations include gene translocations, deletions, and mutations. As discussed above, during meiosis I, homologous chromosomes can undergo crossing over, and during this period, translocations and deletions can occur. The mutations causing 46, XX gonadal dysgenesis, can be sporadic or familial. Mutations in genes coding for the FSH receptor of the ovaries have implications in familial and sporadic cases. Analysis of pedigrees of families with girls with 46, XX gonadal dysgenesis have found an autosomal recessive pattern, although all the possible genes and mutations involved remain undiscovered. A large number of 46, XX gonadal dysgenesis cases have links with the autosomal recessive condition congenital adrenal hyperplasia. Congenital adrenal hyperplasia is most often caused by a 21-hydroxylase enzyme deficiency, which leads to a build-up of the precursor for the enzyme 17-hydroxyprogesterone, which is converted to testosterone, causing virilization. In addition to the genetic causes of 46 XX gonadal dysgenesis, the disorder can also stem from autoimmune disease, infection, and infarct.

Complete 46, XY gonadal dysgenesis is due to the deletion of the SRY gene in 10-15% of cases and due to a mutation in SRY or DDH genes in another 10-15% of cases. True agonadism or a complete lack of gonads is yet another type of gonadal dysgenesis. The exact mechanisms involved are unclear, but mutations in the WT1 gene have been seen in some cases.

Turner syndrome:

Multiple genotypes have been discovered among Turner syndrome patients. The typical 45X type and mosaic types, such as 45X/46XX, 45X/46XX/47XXX, 45X/46XY, are considered partial gonadal dysgenesis. Additionally, some mosaics contain isochromosomes, ring chromosomes, and Xq deletions. Studies have found that as suspected, mosaic forms of the disease tend to have decreased symptoms and phenotypic presentation due to some cell lines having normal genetic information.

The development of Turner syndrome stems from meiotic and mitotic errors that lead to a lack of a second X chromosome. The exact mechanisms that make Turner syndrome so much more common than these other chromosomal disorders are unclear. Still, the belief is that non-disjunction and chromosomal loss during the first few rounds of mitosis in the embryo is the cause. Non-disjunction during mitosis in the early stages of the fetus can also result in the formation of two separate lines of somatic cells 45X/46XX or 45X/46XY. The development of two cell lines of differing genetic makeup is called mosaicism and results in cells across the body having different sets of genetic material, which can also result in different phenotypic presentations in other parts of the body.

Molecular mechanism:

Turner Syndrome results in at least part of the cells of the body lacking a secondary X chromosome. However, normal female cells undergo X inactivation, where there is the utilization of the genes of only one of the X chromosomes. The inactivated X chromosome is turned into heterochromatin that is inactive. This process gets completed by genes in the X inactivation centre near the long arm of the X chromosome Xq. It would be logical to assume that Turner syndrome should have no complications because, after X inactivation, a normal cell has the same amount of genetic material as a Turner syndrome cell, but this is not the case. The reason for this is that about 25% of the genes on the inactivated X chromosome avoid inactivation. Loci on the X and Y chromosome have been mapped that reveal there are pseudoautosomal regions near the end of the Xp and Yp arms that maintain their nucleotide sequence throughout meiotic recombination and the genes in these areas escape X inactivation. These areas are referred to as PAR1 and PAR2.

Multiple genes have now been implicated as candidates to be involved in Turner syndrome. SHOX/PHOG is one of the first genes in the Xp. Yp pseudoautosomal region implicated and is believed to be involved in linear growth. Researchers found a German family with a point mutation in SHOX/PHOG to all have short stature, further implicating this gene in the short stature of Turner syndrome. Although there is evidence there implicating SHOX and short stature, the extent of its contribution to this feature of Turner syndrome has not been established. It appears that SHOX may not be the only factor involved in short stature, and itself may have an effect on other genes that lead to short stature.

Another gene linked to Turner syndrome is RPS4X/RPS4Y; although the data remains inconclusive regarding this gene, it is thought to possibly be a factor in lymphedema and lymphatic abnormalities noted in Turner syndrome. This gene resides in the Yp region of the Y chromosome and has an X-linked homolog that escapes X inactivation.

Another gene linked to Turner syndrome is ZFX/ZFY; it is not thought to be the sole cause of Turner syndrome but part of the gonadal dysgenesis symptoms. Mice studies have revealed that ZFX knockout mice had reduced germ cell numbers and heterozygous female mice showed a reduction in oocytes in comparison to their wild type counterparts but a reduction that was less than what was present in the knockout mice. This pattern of reduction in germ cell/oocyte number is similar to what appears in 45, X Turner syndrome patients versus their mosaic counterparts.

Additionally, recent studies utilizing embryonic stem cells with Turner syndrome have shown additional genes that might have involvement, including pseudoautosomal genes ASMTL and PPP2R3B, which were found to have decreased expression in Turner syndrome cells, and CSF2RA, which the Turner cells showed reduced upregulation. These genes are involved in processes affecting DNA methylation, the cell cycle, and placentation. Lastly, there has been speculation that an X-linked gene DAX1 that suppresses testicular differentiation may cause the gonadal dysgenesis seen in 45X/45 XY mosaics.

46, XX Pure Gonadal Dysgenesis

46, XX complete gonadal dysgenesis is inherited in an autosomal recessive pattern, and several loci and genes have been implicated; however, the exact intricacies of what causes this type of gonadal dysgenesis is unclear.

Inactivating mutations in the FSHR gene coding for the follicle-stimulating hormone receptor is linked to 46, XX dysgenesis, mainly in the Finnish population. Mutation in this receptor leads to blocks in follicular development that cause the follicles to remain in the primary or antral stage. The depletion of the follicles is also seen with this mutation.

Additionally, studies have tried to find other genes that might have specific links to 46, XX gonadal dysgenesis, and the gene BMP15 appears to be a possible candidate. However, a definite link to gonadal dysgenesis remains unaffirmed. BMP15 is a gene that codes for proteins apart from the transforming growth factor-beta family made by oocytes. A rare amino acid substitution at p.A180T in BMP15 was present in a small number of patients with ovarian failure in several studies; additional studies have found that this amino acid substitution may be a rare polymorphism.

The cases linked to congenital adrenal hyperplasia due to 21-hydroxylase deficiency have direct links to over 100 different mutations in the CYP21A2 gene [9]. Regarding premature ovarian failure, a large number of genes, including FMR1, AIRE, FOXL2, and POLG, all share links to distinct syndromes that include ovarian failure among their symptoms. However, there have been no specific links made between these genes and 46XX gonadal dysgenesis.

46, XY Pure Gonadal Dysgenesis

The SRY gene on the Y chromosome essentially is a switch that turns on the processes of testicular development. The other main gene involved in male reproductive development is SOX9, which is involved in the action of Mullerian inhibiting substance. The Mullerian inhibiting substance is involved in inhibiting the development of female internal genitalia and allows for the male development to take place. Additionally, MAP3K1 is also a common gene linked to 46, XY gonadal dysgenesis, and has been reported to be involved in 13 to 18% of patients. MAP3K1 expression downregulates SOX9, which then causes signaling to mirror what occurs in ovarian development leading to abnormal testicular development. The downregulation of the testicular development pathway leads to impaired gonadal development.

Clinical presentation:
Fetal presentation: cystic hygroma, fetal hydrops, heart defect, horse shoe kidney

Newborn: webbed neck, short neck, manifestation due to cardiac defect, skin edema especially edema in dorsum of feet

At puberty: primary amenorrhoea, short stature, webbed neck, widely spaced nipples, cardiac problems such as a bicuspid aortic valve or coarctation of the aorta, horseshoe kidney and sensorineural hearing loss, multiple nevei. Most girls with Turner syndrome tend to have a normal intelligence level but may have issues with verbal and social skills.

Testing:
Chromosomal analysis or karyotype is the test whereby Turner syndrome can be confirmed in clinically suspected cases.

A karyotype involves sending whole blood in a sodium heparin tube to the lab for testing, which may take up to two week, but a rushed result utilizing fluorescence in situ hybridization(FISH) can identify monosomy X in under 24 hours.

Treatment:
Although there is no cure for Turner syndrome, some treatments can help minimize its symptoms. These include:

Estrogen replacement therapy (ERT). ERT can help start the secondary sexual development that normally begins at puberty (around age 12). This includes breast development and the development of wider hips. ERT also provides protection against bone loss.

Combination of estrogen and progesterone to be started after 6-12 months of ERT i.e. after secondary sexual character is well developed. It is also to be started in girls who haven't started menstruating by age 15.

Regular health checks and access to a wide variety of specialists are important to care for the various health problems that can result from Turner syndrome. These include ear infections, high blood pressure, and thyroid problems.

Human growth hormone. If given in early childhood, hormone injections can often increase adult height by a few inches.
The mean adult height in patients with Turner syndrome is 4 ft, 8 in (140 cm); but with growth hormone and estrogen therapy, the average height increases to 5 ft (150 cm). Growth hormone therapy is typically discontinued after the patient reaches a bone age of 14 years; sex hormone therapy is generally continued throughout life.

Guidelines for management of Turner syndrome			
	Investigation	Findings	Treatment
At diagnosis	Blood pressure measurement	If high, Renal evaluation	Antihypertensive
	Karyotype (Chromosomal analysis)	Presence of Y chromosome	Laproscopic gonadectomy to prevent gonadoblastoma
	USG abdomen	Renal malformation	

	Cardiac evaluation and ECHO	Congenital heart defect	
	TSH	Thyroiditis (hypo or hyperthyroid)	Replacementtherapy as per the diagnosis
	Hearing evaluation	Sensory neural hearing defect	Hearing aid if needed
	At diagnosis if older than one year	Strabismus; hyperopia	Ophthalmologic evaluation
		Lymphedema	Support stockings; decongestive physiotherapy
Yearly	Height, weight and BP measurement	Short stature, Obesity and hypertension	
	Ear evaluation	Otitis media	
	TSH and Blood sugar (fasting and postprandial and lipid profile (fasting)	Hypothyroidism, diabetes and hyperlipidemia	As per report
	Liver enzymes	If elevated for more than 6 months	Ultrasonography to evaluate for hepatic steatosis; hepatology consult
	Psychologicalevaluation	Self-esteem; learning issues	Psychoeducational evaluation (schoo based); support
After 4 yrs of age (every 2-4 yrly)	Tissue transglutaminase immunoglobulin A measurement	Celiac disease	
From 7 years and older	Malocclusion and othe tooth anomalies	Orthodontic evaluation	
From 10 years of age to adulthood	Osteopenia; osteoporosis and bone mineral density	Elemental calcium (1,200 to 1,500 mg per day); vitamin D supplementation; appropriate estrogen therapy;	

Conclusion:

Amenorrhoea may be due to gonadal dysgenesis. Though Turner syndrome is the most common cause, other causes like complete gonadal dysgenesis and pure gonadal dysgenesis may contribute to it. Supportive treatment with estrogen therapy, growth hormone and cyclical progesterone and oestrogen is possible. Future reproductive outcome depends upon the cause.

KEY RECOMMENDATION FOR PRACTICE

- Cardiovascular evaluations should be performed at diagnosis to rule out congenital heart defects.
- Ongoing estrogen therapy should be initiated in the preteen years.
- Calcium and vitamin D supplementation should be initiated at 10 years of age.
- If any Y chromosome material is shown on the karyotype, prophylactic laparoscopic gonadectomy is required.
- Short stature should be treated with human growth hormone until the patient reaches a bone age of 14 years.

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8

PREMATURE OVARIAN INSUFFICIENCY

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INTRODUCTION

The human ovary functions both as a reproductive and endocrine gland and both these functions are complementary to each other. Ovarian insufficiency means that the ovary fails to perform its functions. Natural mean age of menopause is around 50 years and when it occurs before the age of 40 it is considered as premature and is known as premature ovarian failure.[1] Primary Ovarian Insufficiency was first addressed by Fuller Albright in 1942.[2] Subsequently, several different terms have been used with variations. In 2011, Cooper and colleagues [3] after an updated search of PUBMED regarding different terminologies being used to define this condition since 1949, recommended the term "insufficiency" instead of "failure." Further, since the term "primary" highlighted that the primary defect of the syndrome lay in the ovaries and secondary ovarian insufficiency indicated a central defect in the pituitary, the term "primary ovarian insufficiency" was agreed upon. To differentiate it from natural menopause an age limit was defined as these women have different needs and management options. The ESHRE special interest group in Reproductive Endocrinology summoned a workshop at Utrecht in 2013 and finally decided the terminology "Premature Ovarian Insufficiency" to avoid confusion as the terms "primary " and "secondary" were used to classify amennorrhea in relation to menarche.

Thus premature ovarian insufficiency is the most widely used term for loss of normal ovarian hormonal and reproductive function in women before the age of 40 because of premature depletion of oocytes .

DEFINITION

The condition is said to be present when a woman who is less than 40 years of age experiences amenorrhea of 4 months or more with two follicle stimulating hormone levels ≥ 30 iu/ml obtained at least one month apart.[4,5]

Hence, it is a state of hypergonadotropic hypogonadism identified by menstrual disturbance with raised gonadotropins and low estradiol levels. This clinical syndrome is characterized by unpredictable fluctuations in ovarian activity in 50 % of women and 5-10% may still conceive spontaneously and deliver a child.[1]

Loss of ovarian reserve in POI can be confused with low ovarian reserve, although these are two separate entities representing different patients with different management needs. Although they lie on the same spectrum, women with POI face challenges much wider than fertility alone .

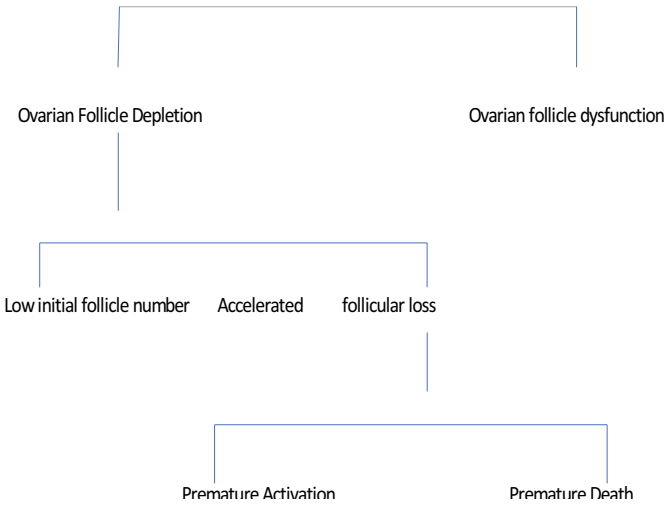
Diagnostic criteria for POI

- Younger than 40 years of age
- Oligo/ammennorrhea lasting 4 months
- Two FSH levels ≥ 30 iu/ml one month apart

ETIOLOGY

The etiopathogenesis of POI is manifold. It could be spontaneous or induced and includes chromosomal, genetic, autoimmune, metabolic, infectious, environmental or idiopathic causes. (Table 1)
The two main pathogenic mechanisms causing POI are - follicle depletion and follicle dysfunction.

Mechanism for POI



In the fetus, germ cells proliferate to form about 7 million oocytes by about 20 weeks of intrauterine life. This number falls rapidly until birth to about 300,000 to 400,000 . These form the follicular pool and co relates with the ovarian reserve The latter can be exhausted prematurely because of inherently low initial numbers or an increased rate of follicular atresia. Low initial numbers can be due to disturbance in any process involving germ cell formation, migration or mitosis and meiosis of oogonia. In mild cases the initial follicle number though low, may still be sufficient to support pubertal development , start of menarche, and in few cases even fertility but ovarian function will deteriorate early in reproductive life. Two functioning X chromosomes are necessary for normal ovarian function. 10-12% of females diagnosed with POI have chromosomal abnormalites of which 94% are linked to X chromosome 6 in form of monosomy /aneuploidy, mosaicism,rearrangements, translocations, X isochromosome and ring chromosome. In the presence of only one X chromosome as in Turners syndrome, ovarian follicular pool is depleted by puberty and the patient presents with primary amenorrhoea but mosaic genotypes such as 45XO/46XX present with secondary amenorrhoea as the rate of atresia is relatively slower. Association between fragile X premutation carrier status and premature ovarian failure is well established with a prevalence of 0.8% in women with sporadic POI and up to 13 % in women with a positive family history.7, 8, 9 However the mechanism by which FMR-1 premutation causes POF is not well understood. Molecular investigations have revealed number of potential genes like FMR1, FRAXE/FMR2, BMP15 for POF on X chromosome though none of them has been accepted as a genetic marker .

POF may also be the result of toxic assemblage as in galactosemia where there is direct toxicity from increased metabolites, aberrant glycolysation of glycoproteins and activation of apoptosis of oocytes. [10]

Autoimmune mechanisms are involved in the pathogenesis of POF and the prevalence is rated to be around 30-40%.[11] Autoimmune oophoritis accounts for less than 5 % of women presenting with spontaneous POI/POF.

Adrenal autoimmunity, clinical or subclinical accounts for 2-10% of POF. [12] The latter may also be a part of autoimmune polyglandular syndromes (APS) when accompanied by other autoimmune endocrinopathies. The association of POF and addison's disease is explained by sharing of autoantigens between ovary and adrenal glands and histological examination of ovarian biopsies in these cases reveal lymphocytic and plasma cell infiltration of the ovary specially around hormone producing cells of the developing follicles.

Other endocrine autoimmune disorders associated with POF are hypothyroidism(13.8%), insulin dependent diabetes mellitus (1.7%),[13] hypophysitis and non endocrine autoimmune conditions like systemic lupus erythematosus, autoimmune hemolytic anemia, vitiligo, rheumatoid arthritis, crohns disease. Parietal cell antibodies in pernicious anemia and acetylcholine esterase antibodies seen in myasthenia gravis can block FSH /LH receptors though the data is not very supportive.

Mutations in FSH and LH receptors located on chromosome arm 2p can also result in follicular dysfunction and hence POF and these patients may present with primary amennorrhoea.
Iatrogenic POF can be caused by radiotherapy, chemotherapy or surgical procedures as hysterectomy and oophorectomy used for malignant or benign diseases. The risk of developing POI after radiotherapy is dependent on dose and age . Similarly, the gonadotoxic effect of chemotherapy is largely drug and dose dependent and is related to age. Any pelvic surgery affecting the vascular supply to the ovary or causing inflammation in that area can lead to detrimental effects later on.

Infections such as viruses like herpes zoster , cytomegalovirus, can lead to ovarian failure as indicated by anecdotal case reports but only mumps oophoritis has been considered to be a cause of POI in 3-7 % cases.[14] Bacteria like Mycobacterium tuberculosis are now known to be established cause of POI.[15]

Environmental toxins like cigarette smoking, alcohol, poor nutrition and exposure to endocrine disruptors like heavy metals, solvents, pesticides, industrial chemicals are implicated in influencing POI but further studies are needed to validate this. [16,17]

Thus several causes for POI have been described but the causative factor remains elusive even after thorough investigations.

Table 1 : Etiology of Premature Ovarian Insufficiency

Genetic (10– 12%)	X – chromosome (94%) – Turner ; Fragile X
Autoimmune	Addison's disease, Thyroid; Coeliac
Environmental	Smoking,Alcohol,Nutrition,Bisphenol A
Iatrogenic	Radiotherapy, Chemotherapy, Excision of B/L endometriomas,B/L Oophorectomy
Infectious	Mumps (3– 7 %)
Metabolic	Classic Galactosaemia, 17 OH deficiency
Idiopathic	

CLINICAL PESENTATION

Clinical presentation of POI is variable and may depend on the etiology. Some women may not experience any symptoms while in others the symptoms may disappear transiently because of fluctuating ovarian function. Irregularity in menstrual pattern is the main presenting feature. Patients with Turner's syndrome or premutation carriers of Fragile X syndrome may present with primary amenorrhea while older age group may present with secondary amenorrhea and symptoms of estrogen deficiency. Hot flushes, night sweats are common but mood variations , vaginal dryness and dyspareunia may also be very disturbing for the patient. Some women may present with infertility as the only complaint.

EVALUATION

Diagnosis is based on presence of menstrual disturbance and biochemical confirmation in women < 40 years of age in the form of oligo/amenorrhea of more than 4 months and an elevated FSH level of > 30 IU/L on two occasions more than 4 weeks apart.

Women with low AMH and regular cycles attending fertility clinics should not be diagnosed as POI . There is no evidence to include ultrasound, laproscopy with or without ovarian biopsy for diagnostic purpose.

History and physical examination

Elicitation of detailed history is important to exclude – the other common causes of amenorrhea like pregnancy, hypothalamic amenorrhea (due to excessive exercise, stress or weight loss), hyperprolactinemia (as suggested by headaches and galactorrhoea) and polycystic ovarian syndrome .

-- Prior pelvic surgeries, irradiation or chemotherapy
--Uterine cause like asherman syndrome
--Symptoms of adrenal insufficiency, hypothyroidism or other autoimmune disorders
--Family history of POI, male mental retardation suggestive of Fragile X syndrome, autoimmune disorders

Patients with early stage ovarian insufficiency may not have any positive physical findings. A physical examination should include
-- height
-- weight
-- body mass index
-- any evidence of galactorrhoea
-- any physical stigmata suggestive of genetic syndrome like short stature , webbed neck , low set ears in Turner's syndrome
-- signs of autoimmune disorders like vitiligo, increased pigmentation of gums as in Addison's disease
-- thyroid enlargement as in Grave's disease
-- changes in pigmentation such as premature grey hair as in autoimmune hypothyroidism
-- presence of hirsutism, acne, stria, acanthosis nigrans and vitiligo .

Investigations

Baseline tests include urine for human chorionic gonadotropin levels to rule out pregnancy. Standard blood chemistry include thyroid profile, prolactin levels, fasting glucose, electrolytes and renal function tests. Other relevant tests can be offered depending on the clinical presentation of the patient. Follow up tests can be done depending on the initial test results. In case of increased initial FSH level, the same should be repeated after 4 weeks to confirm the diagnosis. Serum AMH decline with age in

healthy women but low AMH is more prevalent in POI patients. However, low AMH is also seen in women with poor ovarian reserve having regular cycles . This should not be taken as an indicator of POI but may be done to assess ovarian reserve. Ultrasound should be done for every patient to assess ovarian size, volume, antral follicle count and endometrial thickness but again this modality is for evaluation and plan of treatment and not for diagnosis of POI. 20% patients with primary amenorrhea and 50 % with secondary amenorrhea will respond to progesterone challenge test [18] to evaluate estrogen status but the clinical implication remains doubtful.

Second line investigations (Table 2)

10-12% of women diagnosed to have POI have chromosomal abnormalities and the incidence is higher in females with primary amenorrhea (21%) as compared to those with secondary amenorrhoea (11%).[19,20]

Therefore chromosomal analysis should be performed in all women with non iatrogenic POI. Karyotyping is the gold standard though newer technologies like microarray based comparative genomic hybridisation do exist.

Presence of fragile X premutation can have a bearing on the patient and her family and hence is indicated in all patients of POI. The patients daughters may be carriers and there is a risk of developing POI in grandchildren. Also there is an increased risk of developing fragile X associated tremor/ataxia syndrome(FXTAS) , a late onset neurological problem involving progressive cerebellar gait ataxia and intention tremors in male carriers. This is important from a counselling point of view.

Routine screening of autosomal gene mutations is not recommended unless there is an evidence suggesting a specific mutation (e.g. BPES).

Although presently there is no specific treatment for patients with autoimmune POI , their identification is important to rule out other co existing autoimmune diseases as Addisons disease. Therefore screening for adrenocortical antibodies (ACA) and more specifically 21 hydroxylase (21 OH) autoantibodies, thyroid peroxidase antibodies, anti thyroglobulin antibodies and ovarian antibodies is indicated.If any patient is positive for these antibodies , she should be referred to an endocrinologist and if patient is negative during initial screening, retesting is not indicated unless specific symptoms develop later in life.

Bone density by dual energy x-ray absorptiometry (DEXA) scan should be considered in women with POI as 50% of them are at risk of developing osteopenia.4

Since there is no established cause – effect relationship between viral infections , environmental toxins and POI, routine testing for these is not recommended.

Table 2: Summary of diagnostic work up6

TEST	POSITIVE	NEGATIVE
Karyotyping (to rule out Turners syndrome)	Refer to geneticist, endocrinologist , cardiologist	Repeat karyotype in epithelial cells incases of high suspicion
Y chromosome material	Discuss gonadectomy with the patient	
Fragile X	Refer to geneticist	
ACA/ 21 OH antibodies[1]	Refer to endocrinologist	Repeat in case of clinical signs and symptoms
TPO -Ab[1]	Follow up with TSH annually	

1 *POI of unknown cause or if an immune disorder is suspected*

SEQUELE

POI can have the following long term effects :

1. Psychological effect on the quality of life and self esteem.
2. Early onset Cardiovascular disease and mortality.[21]
3. Osteoporosis in 8 -14% cases causing increased risk of fractures. [4]
4. Neurocognitive decline and Alzheimer's specially in surgical menopause. [22]
5. Infertility in majority of cases.
6. Pregnancy/Obstetric complications. [23]

MANAGEMENT

Management of POI essentially depends upon the needs of the patient, but the psychological well-being and general health must be addressed in all patients. The diagnosis of POI can be emotionally over whelming. It is important to educate and counsel the patient and allow her enough time to accept the diagnosis. Patient needs to be given timely information and options to resolve her problem and a multidisciplinary approach should be taken. An endocrinologist and geneticist may be involved for their specific needs.

Specific treatment is required for

- Premature ageing
- Fertility

Premature ageing

Long term hormonal replacement therapy (HRT) is needed to relieve symptoms of estrogen deficiency (vasomotor, genitourinary symptoms, sexual dysfunction, mood instability issues) and for primary prevention of cardiovascular diseases and osteoporosis. Starting the exogenous hormonal therapy at an early stage is recommended to achieve maximum benefit since longer the duration of estrogen deficiency, the more severe are the sequele. Young women on HRT should continue the therapy till menopause. There after the risks and benefits of continuing the hormones should be reviewed. The main goal of HRT is to mimic normal physiological endocrinology with regards to estrogens. A wide range of HRT formulations are available for oral, transdermal, subcutaneous and vaginal route. In the absence of robust evidence comparing the different types of hormonal therapy in women with POI ,the choice of an HRT regimen should be based on individual preferences considering compliance and the need for contraception as the key factors.

From the limited data that is available , transdermal estrogens may be the preferred route with lower side effects. It has advantages of rapid onset and termination, self administration, achievement of therapeutic levels with lower doses, better patient compliance and avoidance of first pass metabolism. Few studies suggest it to be free of an excess risk of thrombosis.[24] The route of synthetic progestins can be same as that for post menopausal women. Higher levels of progesterone can be achieved in the uterus with lower doses using vaginal route. Moreover vaginal administration of natural micronized progesterone is more effective in creating an “in phase” secretory endometrium after estrogen priming as compared to oral progesterone.[25]

Levonogestrel intrauterine device (Mirena) avoids the adverse effects of oral progestins [26] and allows the usage of estrogen only systemic preparations .

Cyclical combined HRT regimen is preferable for most women with POI specially for those aiming at pregnancy with donor oocytes. This regimen leads to regular proliferation of endometrium , withdrawl bleed and hence regular monthly cycles. This regimen also establishes a normal endometrial development which is required in adolescents with POI with primary amenorrhea. Though some continuous combined HRT regimens may be safer in young women with POI but they are more likely to experience break through bleeding as compared to women of older age group where there is greater uterine atrophy. No progesterone supplementation is required for women with POI and an absent uterus. Dose of estrogen is titrated according to the vasomotor symptoms which may not be the same required for bone or cardiovascular protection. Aim is to achieve the physiological estradiol levels as in women with normal menstrual cycles (50 – 100 pg/ml)[27] and these can be achieved by 100 mcg estradiol given transdermally [28] or 2 to 4 mg per day when given orally. [28] Dose of progestogen will depend on the dose of estrogen and the regimen used .

Data evaluating the risks of various regimens of HRT in young women with POI is scarce and conflicting. Extrapolating the evidence from studies in older women may not be appropriate. HRT has not been found to increase the incidence of breast cancer in young women with POI , however progestins should be given in combination with estrogens to protect the endometrium in women with intact uterus. There was no increased risk of stroke in women using HRT for POI.[7]

Whether androgen replacement should be done in young females with POI remains a controversy. It is seen that in women who underwent oophorectomy at a young age became hypoandrogenic as more than 25 %of androgens in premenopausal females are contributed by ovaries.[29] This can have a deleterious effect on general and sexual health of a female. Though there is not much research on the use of testosterone in women with POI , it can be used in transdermally (gel/patch/cream) or through an implant. A transdermal patch, Intrinsa is being used for women who have undergone bilateral oophorectomy with hysterectomy and face decreased libido.[30]

The general measures including physical activity, adequate diet, calcium and vitamin D supplements, lifestyle interventions like avoidance of smoking and alcohol abuse are advocated. BMD and DEXA scans are helpful in identifying women with osteoporosis who may be benefitted with bisphosphonates. Efficacy of non hormonal modalities is not documented but may be considered in women with contraindications to HRT.

Fertility

Available options are :

- In Vitro Fertilization with Autologous Versus Donor Oocytes or Embryos
- Fertility preservation
- Adoption

It should not be presumed that infertility in women with POI is irreparable as ovarian activity may occur in these women but the likelihood cannot be predicted. There is about 5 % chance of spontaneous resolution and conception and if it occurs then the cause of POI should be considered as it may have implications for the future progeny (e.g. FMR1 premutation). Different treatments in the form of estrogens, gonadotropins and corticosteroids have been tried to increase the natural conception rates without much success.

Fertility preservation may be considered in highly selected cases in females who are at risk for POI because of natural low ovarian reserve (Turners syndrome) or as a result of disease or medical treatment or in sisters of POI patients . Cryopreservation of oocytes, embryos have good success rates and are no longer experimental . In vitro maturation (IVM) is a beneficial method for fertility preservation for reproductive age women who have a contraindication to ovarian stimulation or who are at risk for ovarian hyperstimulation syndrome .

For prepubertal females with cancer or post pubertal patients who cannot delay cancer treatment, cryopreservation of ovarian tissue prior to therapy hold promising results. Cortex of the ovary containing ovarian follicles is cryopreserved via vitrification or slow freezing techniques. The same can be thawed and transplanted to the pelvis (orthotopic transplantation) or extrapelvic subcutaneous tissue such as forearm or abdomen (heterotopic transplantation) at a later stage.

Orthotopic transplantation gives an advantage of a possibility of natural conception while heterotopic transplantation requires an IVF after oocyte retrieval from the extra pelvic site. The main concern regarding transplantation is the fear of reseeding the tumour cells.

For women requiring chemotherapy or radiotherapy, follicular damage can be prevented by gonadal shielding, surgical transposition of the ovaries or oophoropexy, ovarian suppression by GnRH analogues .

The success of these preventive measures will depend on many factors -- women's age and timing being of utmost importance.

The most established option for patients of POI desiring a pregnancy is oocyte donation or adoption. Endometrial preparation with estrogen priming followed by progesterone therapy for making the endometrium receptive needs to be done in these cases before the embryo transfer .Oocytes may be donated altruistically or from a known donor (often a sister) as per the rules and guidelines existing for that country.

Women at an increased risk of maternal mortality or in whom pregnancy is medically contraindicated can opt for gestational carrier.

Fertility Preservation Options

- Oocyte cryopreservation
- Invitro maturation
- Embryo cryopreservation
- Ovarian tissue cryopreservation
- Ovarian transposition
- Gonadal shielding
- Ovarian suppression by GnRH analogues

Future prospects

Preserving oogonial stem cells : Recent research on preserving the oogonial stem cells (OSC) in anticipated cases of POI and then replacing into the ovary later on may revolutionize the fertility practice.

Activation of ovarian follicles : In vitro activation protocols of immature primordial follicles from cryopreserved ovarian tissue of prepubertal girls at risk for POI are still under development . The aim is to increase the number of viable activated follicles available for in vitro growth procedures.[31]

Feto- protective agents : Clinical application of adjuvant therapies like "feto- protective" agents -- sphingosine – 1 – phosphate and granulocyte colony stimulating factor have been shown to prevent chemotherapy induced ovarian damage and follicular depletion but at present their fetoprotective capacity and their potential interaction with cancer therapy is questionable.[32]

Artificial Ovary : The concept is to develop an engineered "artificial ovary" consisting of isolated preantral follicles along with ovarian cells in a 3 D matrix or scaffold . It is an ovarian environment which allows the follicles to grow.[33]

CONCLUSION

Loss of ovarian activity before the age of 40 is the hallmark of premature ovarian insufficiency. It is characterized by hypoestrogenemia and raised gonadotropins. Despite a number of recognised causes for POI, the cause is not identified in a significant number of women. In view of long term health consequences of POI, management should be initiated at the earliest. Appropriate counselling, psychological support and hormone replacement therapy is the cornerstone of care. Since there is a small chance of spontaneous conception, oocyte donation is an established option for fertility . Fertility preservation at a correct time appears as an encouraging modality for those at risk for POI.

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9

ASHERMAN'S SYNDROME

Dr. Sunil Shah

Definition:

Asherman's syndrome (AS) is an acquired condition that refers to the existence of scar tissue in the endometrial cavity . This scar tissue makes the walls of the uterus adhere and reduces the size of the uterine cavity. It is also known as intrauterine synechiae or intrauterine adhesions (IUA). Although the first case was described and published by **Heinrich Fritsch** in 1894, its full description was given much later by Israeli Gynaecologist **Joseph Asherman** in 1948.

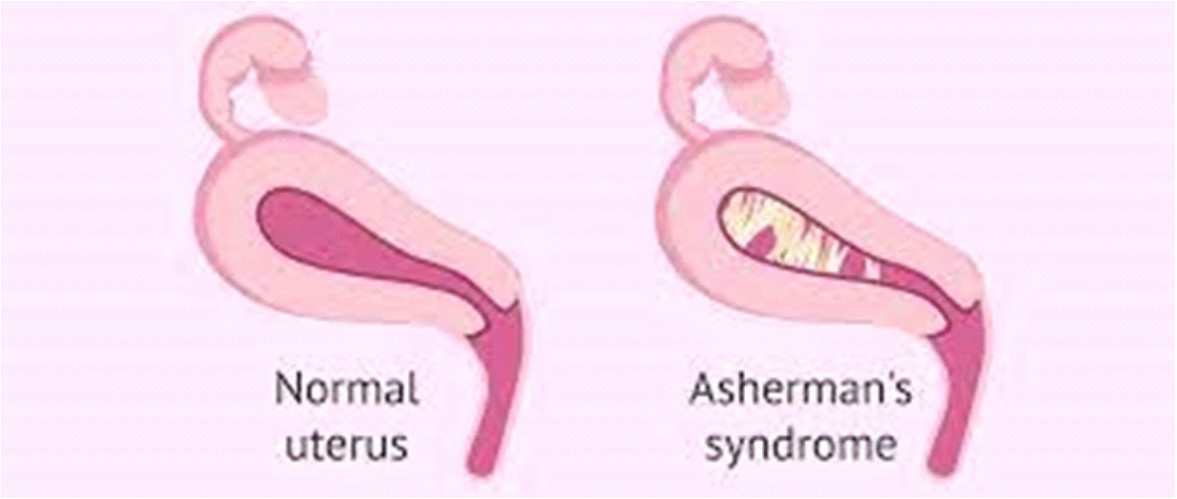

Figure 1: Diagramatic represention oif normal uterine cavity and uterus with Asherman's syndrome

Incidence:

Asherman's syndrome (AS) is an under-reported and under-diagnosed disease.Its actual incidence is impossible to know as most cases are asymptomatic. Only symptomatic patients report to gynaecologists and are investigated. Bharadwaj et al found that 4.6% infertile patients have AS .(1) It is seen in 40%cases of secondary removal of placental residues or repeat curettage following incomplete abortion.(2)* Salzani et al found the incidence of IUA to vary from 15% - 40% after curettage.(3) Some researchers estimate that IUA occurs in nearly 20% women who had dilation and curettage (D&C) or intra-uterine procedures after complications in pregnancy and in postpartum. It is also more frequently found in countries with a high incidence of tuberculosis.

Aetiology

The following predisposing factors or antecedent event can contribute to the *development of AS:-

- Vigorous curettage of gravid or non-gravid uterus accounts for 90 % cases. It can be due to a single D & C or multiple similar procedures. This causes damage to basal endometrium layer leading to IUA. Chances of adhesions are more likely en after post partum or post abortal D&C done two to four weeks after delivery or -abortion. Myomectomy also increases the risk of IUA.
- Scar tissue after Caesarean section or from sutures used to stop haemorrhages is an important cause of IUA. It was seen in 19-27% of women receiving compression sutures to control PPH. (4)
- Acute and chronic infections of the reproductive organs causing endometritis like mycobacterium tuberculosis, chlamydia and schistosomiasis.
- Following septic abortion
- Radiation treatment for carcinoma cervix

Classifications -

AS is classified on the basis various characteristics like site of adhesions, extent of adhesions, vascularity of adhesions and the type of adhesions in the uterine cavity. Toaff and Ballas classified IUA on the basis of appearance of endometrial cavity in HSG in 1978. March's classification by hysteroscopy was also introduced in 1978. The classification of AS introduced by American Fertility Society 1988 is as follows (Table 1):-

Classification	**Condition**		
Cavity involved	<1-3	1/3-2/3	>2/3
	1	2	3
Types of adhesions	Flimsy	Flimsy and dense	Dense
	1	2	3
Menstrual pattern	Normal	Hypomenorrhoea	Amenorrhoea
	0	2	4
Prognostic classification		**HSG SCORE**	**HYSTEROSCOPY SCORE**
Stage 1 (Mild)	1-4		
Stage 2 (moderate)	5-8		
Stage 3 (severe)	9-12		

Table 1: Classification by American Fertility Society, 1988

Types:

Depending on the site and severity of the adhesions, AS is divided into the following types:-

- Intrauterine fibrosis without visible adhesions or obliteration of cavity (Unstuck Asherman's or endometrial sclerosis)
- Cervical canal atresia or atretic amenorrhoea
- Uterine cavity adhesions
  - ▪Central adhesion without obliteration of cavity
  - ▪Partial obliteration and constriction of the cavity
  - ▪Complete obliteration of whole cavity
- Uterine cavity combined with cervical canal adhesion

Clinical Presentation :

- Hypomenorrhea:scanty flow or secondary Amenorrhea usually following dilatation and curettage
- Severe cramping pain during menstruation

Infertility and recurrent implantation failure (RIF) due to insufficient vascularity

- Recurrent pregnancy losses (RPL)
- Placenta previa and placenta accreta
- Intra-uterine growth retardation

Diagnosis:

The following initial investigations help to rule out the different causes of amenorrhea or hypomenorrhea

1. Urine pregnancy test
2. Hormonal assays to rule out PCOD, Menopause either premature or regular
3. Pin hole cervix: Cervical sound insertion

Various imaging studies can detect the intra uterine adhesions, but complete information and therapeutic interventions can be done by hysteroscopy only.

1. Hysterosalpingography. This has a sensitivity of 75 to 81% with a specificity of 80%. (12) The extent and location of synechiea can be easily seen in HSG . The radiographic image depends on the site and severity of disease.(5) IUA typically shows multiple,irregular linear filling defect .When there is extensive symmetrical obliteration of uterine cavity the uterus may appear small and in severe cases cavity is not visualised at all.

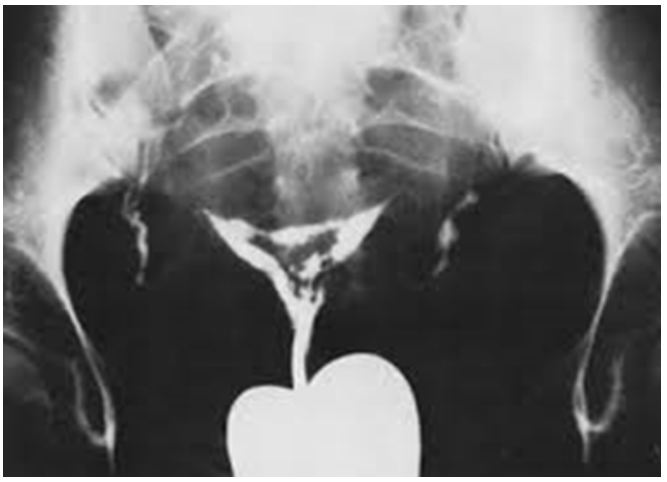

Figure 2: Hysterogram of uterus with Asherman's syndrome6666666

2 D and 3 D USG with Colour doppler: a very thin irregular echogenic endometrium with very little or no colour flow in the base is usually seen . Different sizes of endometrial cavity may be seen at different level.

3.Saline infusion sonography (SIS) / Sonohysterography : SIS uses saline solution that flows into the uterus to make imaging clearer. It is a safe and accurate method of endometrial cavity evaluation.(6)

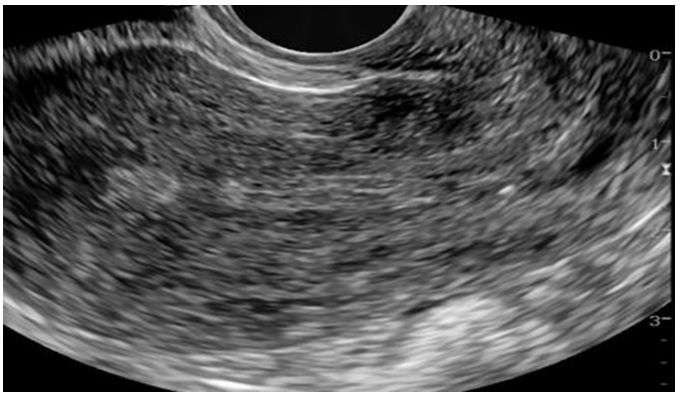

Figure3: 2D Ultrasound showing Asherman's syndrome

4. Hysteroscopy. The best way to diagnose and manage Asherman's syndrome is hysteroscopy. IUA can be easily diagnosed and treated in the same sitting. The European Society for Hysteroscopy classification of intrauterine adhesions grades AS as follows:-

Grade	Description
I	Flimsy, thin or invisible. Easily ruptured by hysteroscopic sheath alone Cornual areas normal
II	Singular firm adhesions Connecting separate parts of the uterus Visualization of both ostia possible Cannot be ruptured by sheath alone
IIa	Occluding adhesions only in the region of the internal os Upper uterine cavity normal
III	Multiple firm adhesions Connecting separate parts of the uterus Unilateral obliteration of ostial areas of tubes
IIIa	Extensive scarring uterine cavity wall with amenorrhoea or severe hypomenorrhea
IIIb	Combination of III and IIIa
IV	Extensive firm adhesions with agglutination of uterine cavity walls Occlusion of both the ostia

Table 2: TheEuropean Society for Hysteroscopy Classification of Intra-uterine adhesions

5. MRI: This can be of use when adheshions involve the endocervical canal.
6. Investigations to detect tuberculosis, chlamydia or schistosomiasis.

Guidelines for diagnosis of intrauterine adhesions (13)
1.Hysteroscopy is the most accurate method for diagnosis of IUAs and should be the investigation of choice when available. Level B evidence.
2.If hysteroscopy is not available, HSG and SHG(SIS) are reasonable alternatives. Level B evidence.
3.Magnetic resonance imaging should not be used for diagnosis of IUAs outside of clinical research studies. Level C evidence.

Management: The management strategy mainly depends upon:
A. Dilatation and curettage: This is no longer used as a treatment modality. It can further aggravate the adhesions .
B. Hysteroscopic resection of intra-uterine adhesions: The goal of treatment is to make the uterus regain its normal size and shape. The magnified and direct view of intrauterine adhesions allows a safe and immediate treatment. In addition to diagnosis, hysteroscopy can also be used to treat IUA by cutting the adhesions with very small scissors, lasers, or other types of instruments that use hooks or electrodes. The tip of the hysteroscope along with uterine distension usually breaks down the filmy adhesions.7 As a rule adhesions are removed from the lower part of the uterus to the upper part8. Flimsy and central adhesions are dealt first followed by lateral and dense adhesions.9

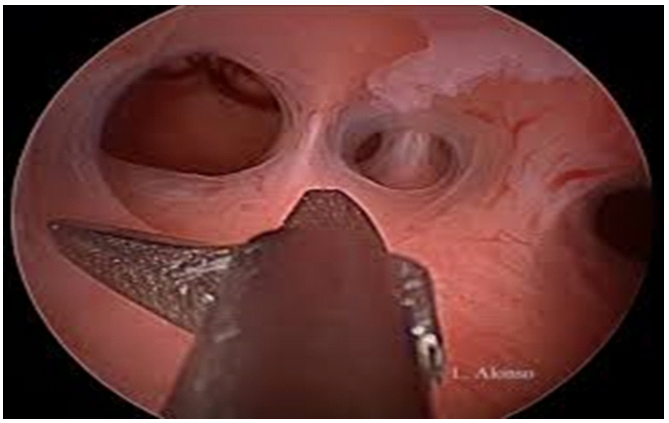

Figure 4: Hysteroscopic view of intra-uterine synechiae

● Use of a sharp needle **(Touhy needle)** or - do not cause thermal damage to the residual endometrium and has lesser chance of perforating the uterus during surgery. It is done under fluoroscopic guidance under general anesthesia and image intensifier control .
● **Thermal energy or laser source** are also efficient for hysteroscopic adhesiolysis but can lead to damage of the residual endometrium. 8,10,11
● **Other hysteroscopic techniques:** This technique is usually used in treatment of severe cohesive IUAs when routine hysteroscopically directed adhesiolysis is not possible . It is effective in creating cavity in severe IUAs. In this technique, after dilating cervix with dilator and using glycine as the distension medium ,several myometrial incisions , 4-mm-deep are created with a Collin's knife electrode from the fundus to isthmus.14 A simultaneous laparoscopy may be performed to observe the distal end of the tube in patients with history of pelvic inflammatory disease or ectopic pregnancy. After the procedures, estradiol is given to prevent re formation of adhesions. In cases of cervical stenosis, the procedure can be done under ultra sound guidance to prevent creation of false passage and uterine perforation .
● **Hysterotomy:** If adhesions are severe and the uterine cavity cannot be entered then laparotomy followed by hysterotomy may be done. This is rarely done in current practice.

After adhesiolysis the one or more of the following measures may be taken to prevent reformation of intra-uterine adhesions:-
a. Mechanical separation of anterior wall and posterior wall by an intrauterine contraceptive device followed by hormonal therapy for regeneration of the endometium: Intra uterine device, Foley's catheter (pediatric size) or uterine balloons and different types of gels are used.. Supplementation with 4-6mg of estradiol for 30 days along with medroxyprogesterone acetate 10mg in the last 10 days of estradiol supplementation is given.6
b. Anti-Tuberculous therapy: If hysteroscopic finding suggest endometrial Koch's infection then ATT is given in full dose and regime.

c. Treatment of PID for chlamydia with Doxycycline is started6.

d. Hyaluronic acid: In the past decades hyaluronic acid wa6s used to prevent intraperitoneal and intrauterine adhesions formation.

Newer interventions to restore normal endometrium include the following :

a. Pharmacological interventions: Estradiol valerate, Sildenafil and Nitric oxide.

B. Stem cells transplantation intra-uterine infusion of autologous stem cells: Endometrial cells has intrinsic capacity to regenerate. Endometrial tissue contains progenitor cells, mesenchymal and stromal cells. Intra. Preliminary study suggests good outcome but data to date is insufficient to recommend regular use of this therapy .

C. Fresh platelet rich plasma (PRP): Intra- uterine infusion of freshly prepared PRP along with estradiol valerate 12 mg. This can be repeated after 72 hours. So far this is being mostly used is research settings.

Post-operative assessment

Diagnostic hysteroscopy and repeat surgery if required is done mostly after three months of the initial procedure.

Outcomes

It is measured in terms of menstrual blood flow, pregnancy rates and its outcomes. The more severe the disease, the poorer is the outcome after adhesiolysis . In a retrospective cross-sectional study of 357 women3, the pregnancy rates after adhesiolysis were 61 percent in mild IUA, 53 percent in moderate IUA, and 25 percent in severe IUA. 15 The mean time to conception was 9.7± 3.7 months. Miscarriage ,Intrauterine growth restriction, preterm delivery, abnormal placentation is more common in these patients.

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