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Primary Amenorrhoea

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Abstract

The amenorrhoea is the normal physiological feature in prepubertal girls, failure to commence menstruation is primary amenorrhea. A normal uterovaginal anatomy and functional hypothalamic pituitary ovarian (HPO) axis is essential for menstruation. The detailed relevant medical and family history along with thorough physical examination adds in for requesting relevant investigations to find out the cause. In the absence of secondary sexual characteristics, hormonal disturbances are the most likely cause while anatomical problems are more common in the presence of secondary sexual characteristics, along with physiological delays and endocrinopathies. Investigate primary amenorrhoea without secondary sexual development at 13 years and with secondary sexual development at 15 years of age, consider early referral if suspicion of chromosomal abnormality, hyperandrogenemia, anatomical abnormalities or primary amenorrhoea persists for five years after thelarche. The multidisciplinary team approach, to support patient and parents with evidence base knowledge for decision-making is the corner stone. It is important to address patient and their family needs, individually for the best outcome.

Keywords: HPO Axis Problems, Genital Anatomical Problems, Hyperandrogenism, Hyperprolactinaemic

Introduction

The prevalence of primary amenorrhea is about 0.3% [1, 2]. The environmental factors, chronic physical health issues, organic HPO axis issues and anatomical problems is a part of the hierarchy to investigate amenorrhoea. These can affect the HPO axis function directly or indirectly, results in amenorrhoea. The understanding of normal cyclical release of hormones during menstrual cycle helps to find out the underlying cause.

The causes can be divided broadly into:

- hypothalamic and pituitary
- primary ovarian insufficiency due to chromosomal problems
- genital tract development problems
- hyperandrogenaemia

Normal physiology for menstruation

The normal functioning hypothalamic pituitary ovarian (HPO) axis is crucial for menstruation. HPO axis includes, normally functioning hypothalamus, pituitary, and ovaries with intact feedback loops. Pituitary gonadotrophins (GnRH) pulse release is mainly nocturnal between 8 and 13 years of age, near puberty day time GnRH pulse frequency outpace the nocturnal release and approaching the adult pattern at puberty [3]. Disruption at any level in this axis (Fig 1) results in amenorrhoea. This disruption may be organic or functional.

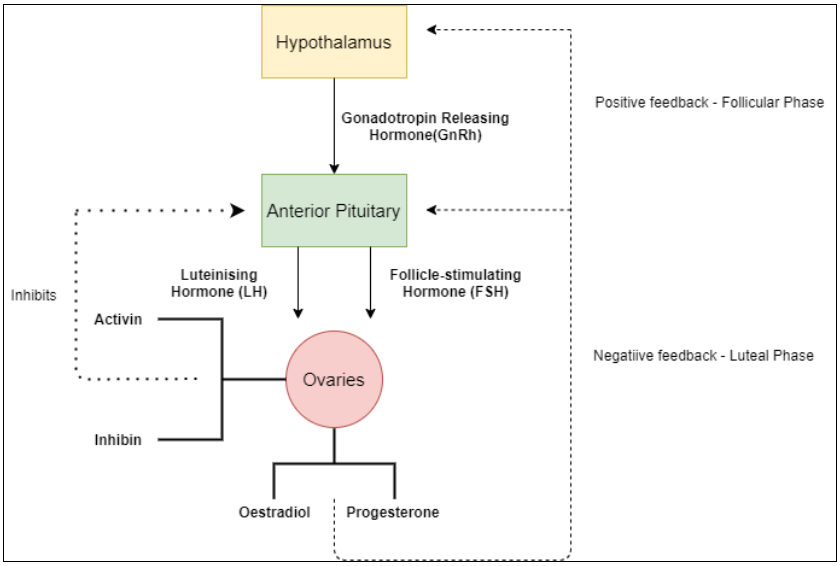

Fig 1: Functional endocrine axis comprising of hypothalamus, pituitary, and ovarian hormonal regulation

This cyclical activity of hormonal release is usually not regular during the first one or two years after puberty and cycles are frequently irregular and anovulatory.

Materials and methods

We used electronic data base, MEDLINE, EMBAS, PUBMED, Cochrane central register for controlled trials, conference abstracts and British library from Jan 1995 till June 2021. We used articles in English language. The terms used for search: Primary amenorrhoea, failure to achieve menstruation, amenorrhoea with anatomical problems, amenorrhoea with abnormal chromosomes karyotype, hyperprolactinemia, hyperandrogenemia, Androgen insensitivity syndrome, HPO axis, FHA, chronic illness and constitutional delay. Initial search comes up with 2000+ articles, all articles screened and duplications excluded by title and key words. 301 abstracts reviewed and 157 articles full papers were reviewed and finally 92 articles were included in this review.

See figure 2:

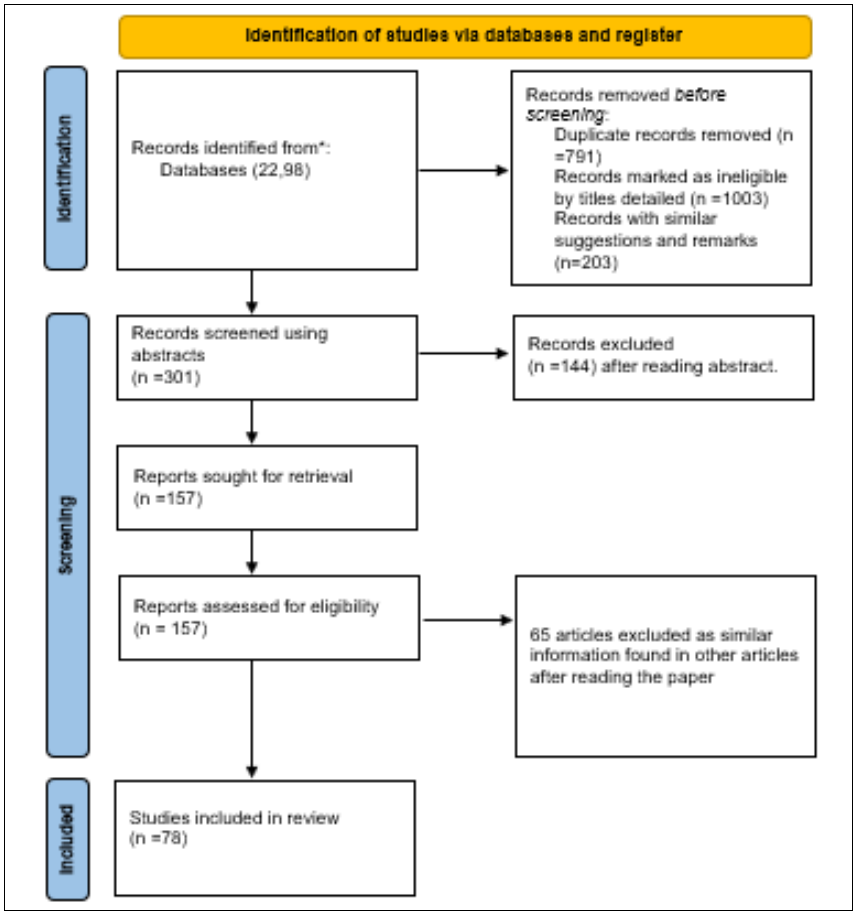

Fig 2

The detailed history, thorough clinical examination and relevant investigations help to find the cause for amenorrhoea.

History taking

It is important to take a detailed history to evaluate emotional stress, mother and sister's gynaecological history, family history of diabetes, genetic disorders, delayed puberty, symptoms of thyroid dysfunction and glactorhoea, weight loss / gain, hirsutism, anosmia, chronic systemic diseases, and previous treatment with radiotherapy or chemotherapy. Ask specifically about sexual history, contraception, cyclical lower abdominal pain, details of gynaecological surgical procedures, a vaginal or uterine surgery and medications. Substance misuse especially cocaine and opiates should be excluded.

Examination

The puberty starts usually at 11 years of age with breast bud development (thelarche), followed by pubarche (first pubic hair then axillary hair growth), accelerated growth and menarche. The menstruation occurs in approximately two to two and a half years after thelarche. The pubarche is independent of GnRH function and influenced mainly by dehydroepiandrosterone [3].

Table 1: Tanner stage for females

Tanner classification	Breast	Pubic hair
Tanner I	The areola follows the skin contours on chest no glandular tissue (prepubertal)	No pubic hair (prepubertal)
Tanner II	Areola starts to widen and appearance of glandular tissue	Pigmentation appears in labia majora small amount of thin pubic hair.
Tanner III	Breast and areola continue to widen and elevate and breast contour remains normal	Pubic hair starts expanding laterally and texture becomes coarse and curly
Tanner IV	Papillary and areola growth continues along with secondary mound development of overall breast tissue	Extension of pubic hair from pubis to medial thighs and texture of hair is almost like adult
Tanner V	Adult size breast with areola recession and papilla extends little above the breast contour	Adult texture hair extends to medial surface of the thighs and inverse triangular appearance superiorly

A Paediatrician James Tanner defines the stages of puberty in children using breast size, external genitalia, and pubic hair growth, known as Tanner staging. See Table 1.

Through examination using Tanner scale, look for features of Turner's syndrome, Cushing's syndrome, thyroid dysfunctions and hyperandrogenemia. The vaginal examination for external genitalia an ultrasound scan can add further to diagnosis.

At 13 years of age; a female has failed to achieve tanner stage 2; breast development is delayed puberty [4].

Investigations

In sexually active patient's rule out pregnancy and follow Table 2 for the relevant investigations for each case.

Table 2: Investigations with expected results in relation to the underlying condition associated with primary amenorrhoea

Condition	Follicle stimulating hormone (FSH) /AMH	Luteinizing Hormone (LH)	Prolactin	Androgens (testosterone, 17-OHP, Cortisol	Ultrasound scan (Uterus)	Chromosome / Genes	Breast development	Pubic hair
Constitutional delay	↓	↓	↓/ ↔	↓/ ↔	P	46XX	Delayed	Delayed
Turner syndrome	↑	↑	↔	↔	P	45X0/(45X0,46XX	delayed	Delayed
Gonadal dysgenesis Perrault syndrome	↑	↑	↔	↓ / ↔	P	46XX	delayed	delayed
Gonadal dysgenesis Swyer syndrome	↑	↑	↔	↓	P	46XY	delayed	delayed
Mayer-Rokitansky-Kuster Hauser (MKH)	↔	↔	↔	↔	A	46XX	N	N
Complete androgen insensitivity (AIS)	↔	↔/↑	↔	↑	A	46XY	N / As	A
Congenital adrenal hyperplasia (CAH)	↔/ ↓	↔/ ↓	↔/↑	↑/ ↑17OH progesterone	P	46XX	N	N
Cushing's syndrome	↔/ ↓	↔/ ↓	↔/↑	↑ / ↑ Cortisol	P	46XX	N	N
Thyroid dysfunction	↓	↓	↔/↑	↔	P	46XX	N /D	N/ D
Pituitary adenoma (Hyperprolactinemia)	↓	↓	↑	↔	P	46XX	N/ D	N/ D
Congenital Hypothalamic hypogonadism (HH)	↓	↓	↑	↔	P	46XX	D	D
Acquired HH	↓	↓	↑	↔	P	46XX	D	D
Hypopituitarism	↓	↓	↓	↔	P	46XX	D	D
Polycystic ovary syndrome (PCOS)	↔	↔ /↑ slightly in 40% cases	↔ /↑ slightly in 5-30%	↔ /↑ marginally raised	P	46 XX	N	N
Premature ovarian insufficiency (POI)	↑	↑	↔	↔	P	46XX, 46XY 45X0, 47XXX, FMR1 gene	D/N	D/N
Functional Hypothalamic Amenorrhoea (FHA)	↓/↔	↓/↔	↔	↔	P	46XX	D /N	D/N

P- Present, A---Absent, N----Normal, D------delayed, As-----asymmetrical, Antimullerian Hormone (AMH), 17-OH progesterone (17-OHP)

Serum Antimullerian Hormone (AMH) is considered more reliable than serum FSH for ovarian reserve determination. The result of AMH is independent of the cycle, very low levels in the presence of amenorrhoea suggests premature ovarian insufficiency (POI) [5].

The serum FSH < 5IU/L suggests a hypogonadotropic condition seen in prepubertal girls and in hypothalamic and pituitary dysfunction. A high FSH >20IU/L suggests a hypergonadotropic state such as menopause. FSH and AMH are normal with adequate ovarian androgens and chronic anovulation the likely causes are hyperprolactinemia and thyroid dysfunction.

Women should be advised to wait at least 48 hours after breast examination before having a serum prolactin blood test. Where serum prolactin levels >500mIU/ml and less than 1000mIU/ml, repeat the test. Hyperprolactinaemia may occur in the presence of stress, hypothyroidism, renal impairment and PCOS. Medications including antipsychotics e.g. risperidone raise prolactin levels as does metoclopramide and domperidone. If prolactin level > 1000 mIU/ml an magnetic resonance imaging (MRI) should be arranged and referral to endocrinologist for further evaluation e.g. MRI with contrast for tumours, haemorrhage and vascular abnormalities [6, 7]. Furthermore, visual acuity, visual field assessment and optic disc examination will be required in symptomatic cases.

Elevated testosterone levels >5 nmol/L requires further investigation to exclude androgen insensitivity syndrome (AIS), androgen secreting tumours, Cushing's syndrome and late onset congenital adrenal hyperplasia (CAH). A serum testosterone level of 2 nmol/L- 5 nmol/L is associated with polycystic ovary syndrome (PCOS) [2].

Radiological tests including trans abdominal ultrasonography have a limited role. Trans vaginal sonography provides more detailed information of ovarian morphology and possible upper genital tract malformations like absent uterus etc. If required MRI provides more detailed imaging of the genital tract.

Chromosome karyotype will confirm the diagnosis in cases where suspicion arises on physical examination, radiological and biochemistry results for congenital problems like Androgen insensitivity syndrome (AIS), Swyer and Turner syndrome. In cases of suspected POI request fragile X mental retardation gene (FMR 1) sequencing along with chromosomal karyotype [8].

Routine screening for autoantibodies for ovarian pathology is not recommended [1].

Causes

The causes can be divided into two groups for description: Amenorrhoea in the presence of normal development of secondary sexual characteristics and with absent or impaired development of secondary sexual characteristics.

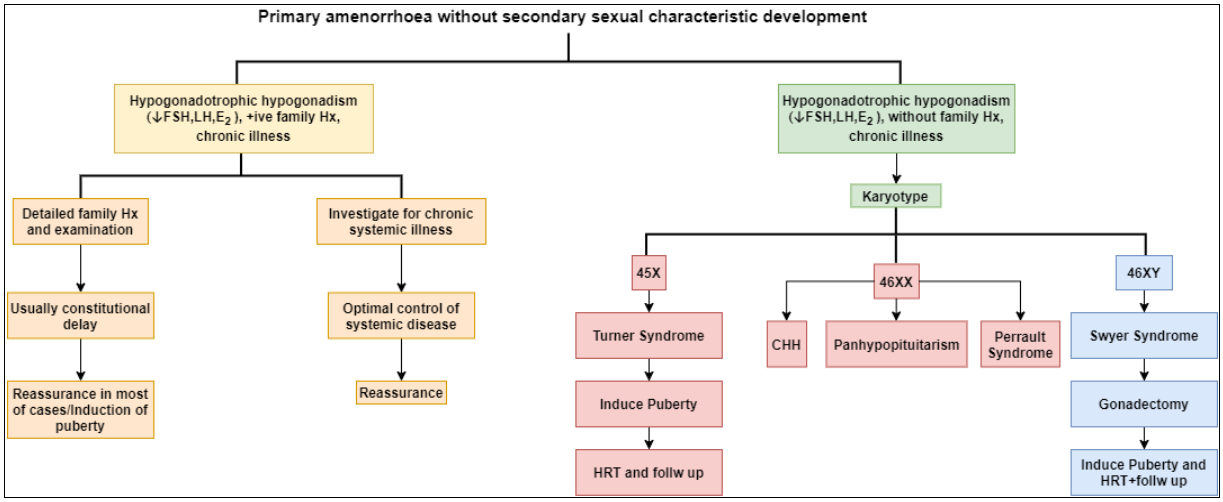

Fig 3: Flow chart for Primary amenorrhoea causes with absent or impaired secondary sexual characteristics

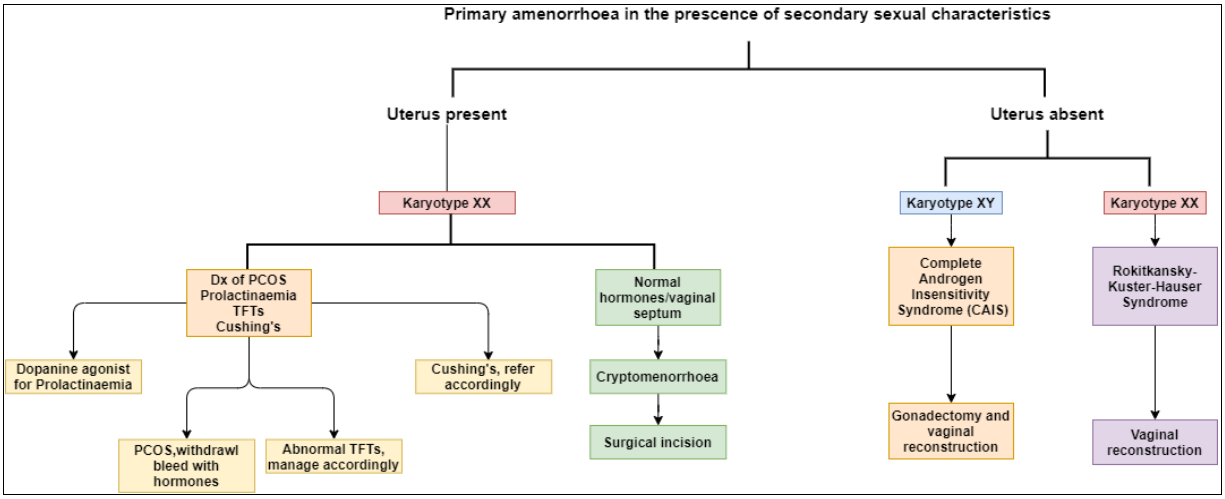

Fig 4: Flow chart for Primary amenorrhoea causes with normal or impaired development of secondary sexual characteristics

Hypogonadotrophic hypogonadism

Constitutional delay

The delayed maturation of hypothalamic-pituitary ovarian (HPO) axis results in delayed puberty. Usually, positive family history of similar symptoms in the mother or elder siblings. The examination confirms a delay in the skeletal growth and sexual maturity, compared to the peer group and accounts for 30%-56% of primary amenorrhea cases [9]. Reassurance and expectant management with healthy life style advice is usually sufficient.

Hypothalamic and pituitary disorder

Functional Hypothalamic Amenorrhoea (FHA)

FHA is the diagnosis of exclusion, the endocrine society criteria for the diagnosis is menstrual cycles > 45 days or amenorrhoea for 3 months, weight loss, excessive exercise or stress and hypogonadotropic hypogonadism, negative progesterone challenge test and normal MRI brain [10]. The physical, emotional and nutritional stress leads to suppression and abnormal pattern of pulsatile gonadotropin secretion and anovulation [11]. An intense psychological response to life events, less body fat or excessive weight loss over short period results in FHA [11].

Eating disorders results in dysfunctional hypothalamic control of appetite, thirst, temperature, sleep, autoimmune and endocrine. The leptin from adipose tissues in the central nervous system help to regulate eating behaviour, energy balance and GnRH production [12]. The leptin is usually low in lean amenorrhoea women than menstruating women. The malnutrition and oestrogen deficiency results in low bone mineral density (BMD) and bone fractures.

Chronic physical and sexual abuse, emotional deprivation and illness like hypothyroidism, type I diabetes, chronic renal failure, congenital cardiac disorders, cystic fibrosis, sickle cell anaemia and thalassemia may result in dysfunction of HPO axis [17, 18]. In chronic conditions, an adaptive response results in FHA and hypogonadotrophic hypogonadism, amenorrhoea help with metabolic energy balance and delayed puberty [10]. Epilepsy and antiepileptic medications result in hypothalamic disturbances or hyperprolactinemia [19]. The treatment of the underlying cause usually restoration normal HPO axis and menstruation.

The behaviour changes, reduction in exercise and healthy eating results in restoration of metabolic and endocrine function in the majority but one-third remain amenorrhoeic [20]. The hospital admission is required in life threatening severe energy and electrolyte imbalance situations. National institute of clinical excellence (NICE) recommends BMD testing for undernourished women [21]. The non-pharmacological therapy for a year and transdermal 17β oestradiol can be tried for short duration only. The endocrine society does not support the use of combined oral contraceptive (COC) pills, bisphosphonates, testosterone and leptins for increasing BMD in adolescents with FHA but COC can be used for contraception [10].

Congenital Hypothalamic Hypogonadism (CHH)

The CHH is affecting 10-20% of adolescents more common in male than females (5:1) [23]. CHH presents with GnRH deficiency, incomplete or absent pubertal growth [22]. An embryonic developmental problem with impaired sense of smell and failure to achieve puberty is known as Kallman syndrome. The distinguishing features between constitutional delay and Kallmann syndrome is the presence of pubic hair and inability to perceive smell.

The CHH associated phenotypes include Prader–Willis syndrome, Laurence–Moon syndrome and Gordon Holmes syndrome. The presentation of CHH is similar to constitutional delay. The diagnostic work up includes genetic chromosomal testing, MRI brain, ultrasound for genital organs, BMD and the standardised smell tests to exclude olfactory causes as 50% of CHH have no smell or reduced smell though self-reporting is underestimated [27]. These cases need puberty induction.

Acquired Hypogonadotrophic hypogonadism (AHH)

The pituitary adenomas are rare cause for AHH in adolescence, but the commonest cause in adults and almost always benign along with craniopharangiomas, meningiomas, gliomas, chordoma, epidermoid cyst, Rathke's cleft cyst and metastatic tumours. [29]. Other causes are pituitary fossa surgery, radiation, ischaemia and infarction, infiltrative disease like lymphocystic hypophysitis, sarcardosis, tuberculomas, syphilis and heamochromatosis [28]. The commonest are prolactinomas (46%-66%), followed by corticotropinomas (30%), somatotropinomas (5-15%), gonadotropinomas, thyrotropinomas and non -functioning adenomas [30].

The impaired production or secretion of GnRH or gonadotropin directly or via hyperprolactinaemia that interferes with the dopamine inhibitory effect results in AHH [9]. Adenomas of 10mm or less are known as microadenoma, more than 10mm are macroadenoma. The magnetic resonance imaging (MRI) brain with gadolinium contrast is recommended for diagnosis [34].The classical presentation is bitemporal hemianopia and nonspecific headache in macoadenomas. In symptomatic macroadenomas trans-sphenoidal resection followed by pharmacological therapy while with microadenomas pharmacological treatment with cabergolin or bromocriptine is the usual treatment [30, 35]. The normal prolactin levels resume menstruation, ovulation and fertility.

The non- functional adenoma do not shrink with pharmacological treatment. A persistent mild rise in prolactin levels with no signs of hyperthyroidism, acromegaly or Cushing's syndrome is associated with non-functioning adenoma [35].

Primary hypothyroidism may present with hyperprolactinemia due to thyrotroph and lactotroph overgrowth in the pituitary gland. [37, 9]. Chronic renal impairment results in a steady rise in serum prolactin due to defective renal clearance, increased production due to dopamine suppression [31]. The treatment of the underlying cause lowers the prolactin levels and restores menstruation.

Certain medications affect directly to inhibit GnRH secretion or via hyperprolactinemia or reduced pituitary response to GnRH or hypohysitis. Opiates reduce LH production and lead to clinical hypogonadism [38]. Neuroleptic medication has more affinity for dopamine receptors and blocks the inhibitory effect of dopamine resulting in hyperprolactinemia[10]. Antipsychotics especially risperidone and selective serotonin reuptake inhibitors (SSRI) like fluoxetine cause hyperprolactinemia [35]. Metoclopramide, domperidone and antihypertensive like methyldopa, verapamil and calcium channel blockers decreases dopamine secretion resulting in modest hyperprolactinemia [36].

Hypopituitarism

The reduction in production and secretion of hormones from anterior or posterior pituitary is called hypopituitarism. Hypothalamic pituitary (HP) axis can be damaged due to infection, inflammation, ischaemia, haemorrhage or brain trauma [39]. The hypophysitis (inflammation of the pituitary) is very uncommon, there are some case reports during pregnancy and early adolescents with primary amenorrhoea [39].

In idiopathic hypopituitarism, consider infiltrative causes like haemochromatosis, lymphocytic hypophysitis, sarcoidosis and tuberculosis. These may present with reversible or permanent hypogonadotropic hypogonadism; treatment of underlying cause restores the function [41].

Ischaemic damage to the pituitary gland after massive post-partum haemorrhage due to hypovolemic hypotension known as Sheehan's syndrome is usually a case of secondary amenorrhoea. The symptoms vary due to the extent of the damage to the pituitary gland.

The pituitary gland is located in the sella turcica, at the base of the brain. The empty sella syndrome (ESS) is a misleading term actually a congenital defect in the sellar diaphragm and subarachnoid space and CSF extend into the sella and appears as ESS. Secondary ESS is usually iatrogenic after surgery or radiation to the pituitary adenoma. Patients with ESS are usually asymptomatic but may present with hypopituitarism. It is more common in obese and hypertensive women with amenorrhoea [43].

It is important to assess the structure and function by blood tests for full HP axis. The pituitary function can be assessed by checking serum prolactin, cortisol, insulin-like growth factor 1 (IGFR 1), thyroid stimulating hormone (TSH), free thyroxine, luteinising hormone (LH), follicle stimulating hormone (FSH), testosterone and oestradiol. The blood sample should be taken in the early morning [29]. MRI imaging of the pituitary gland for anatomical causes.

The hydrocortisone is the first line therapy in 98% of cases followed by replacement of deficient hormones like thyroxine, sex steroids, GH and desmopressin [40]. There should be regular surveillance for patient's wellbeing to assess the BMD and treat the underlying cause [39].

Genital tract problems

The genital tract problems are usually by birth, rarely following surgical complications. The female genitalia develops from the medial migration and midline fusion of the Mullerian (paramesonephric) ducts into uterus, fallopian tubes, cervix and upper one third of the vagina. The lower two thirds of the vagina develops from the urogenital sinus invagination and join the Mullerian system vertically to complete the tract. The hymen develops by invagination of the posterior vaginal wall of the urogenital sinus. Mullerian abnormalities range from vaginal, cervical and uterine agenesis to vaginal septum and imperforate hymen.

An imperforate hymen usually presents with primary amenorrhoea and cyclical lower abdominal pain or urinary retention. On vaginal examination, a bulging membrane at the lower limit of introitus and valsalva manoeuvre make it more pronounced to facilitate the diagnosis. The treatment is incision and drainage without any long-term consequences [46].

A transverse vaginal septum occurs when the vaginal plate formed from the sinovaginal bulb fails to break down during embryogenesis. In young girls on examination, cervix is not visible with short vagina and heamatocolpos (poling of blood behind the spetum) is common. Thorough evaluation for septum thickness and distance from the introitus via MRI is helpful. The septum is <3cm from introitus in 75% of cases and very rarely it is >6cm, almost half of septi are > 1cm thick [47]. The patients should be managed in a centre of excellence. The use of continuous COCP or GnRH can help to alleviate pain. Endometriosis is common in these cases due to the retrograde menstruation [44].

Cervical agenesis is very rare, results in haematometra (blood in the uterus) and retrograde menstruation leading to endometriosis and adhesions in the pelvis [48]. Cervical stenosis with complete outflow obstruction is a rare complication after cervical surgery.

Asherman syndrome is suspected in cases with a history of uterine surgery followed by secondary amenorrhoea. The typical presentation is hypomenorrhoea followed by amenorrhoea and poor or no response to sequential treatment with exogenous estrogen (1.25 mg daily) for 21 days and progestin (medroxyprogesterone (MPA) 10mg daily for 5-7 days). This demonstrates endometrial failure and aids to the diagnosis.

Mayer-Rokitansky-Kuster Hauser (MKH) Syndrome

Mullerian agenesis is the failure of mullerian duct development results in rudimentary or absent uterus, cervix and a short vagina depending on the level of the defect. In MKH syndrome uterus is absent or rudimentary with upper one third of vagina, normal secondary sexual characteristics and 46XX karyotype. The prevalence is 1:5000 cases [45]. The majority of cases present with primary amenorrhoea, only few present with haematometra [49].The ovaries are usually normal and located bit higher in the pelvis. MKH is associated with renal abnormalities like unilateral renal agenesis or horse shoe kidney, vertebral problems like hemivertebrae, cardiac and hearing abnormalities [49, 50].

The treatment involves creation of functional vagina with vaginal dilators or construction of a neovagina to facilitates coitus if desired [50]. The ovaries are functional and ovarian reserve is assessed by serum AMH. A small proportion of MKH women and their mothers have gene associated with classical Galactosaemia [51] that increases the risk of POI. The pregnancy options include surrogate gestation or uterine transplant [50]. All clinicians should adopt a sympathetic and sensitive approach to address this issue with patients and their parents. Signposting to support groups and websites e.g. https://www.mrkh.org.uk.

Androgen insensitivity syndrome (AIS)

Complete AIS (CAIS) is also known as testicular feminization or male pseudohermaphroditism. The prevalence is 4/100,00 [54]. The karyotype is 46XY and male gonads produce both testosterone and AMH [52]. AIS is third most common cause of primary amenorrhoea after gonadal dysgenesis and mullerian abnormalities. The mutation at androgen receptor (AR) gene on the long arm of the X chromosome results in end organ insensitivity to androgen action [53]. The serum testosterone is high and normal conversion to dihydrotestosterone with normal or high serum LH. Almost half of the cases are X linked recessive inheritance and half are new gene mutations in maternal X chromosome [52]. CAIS presents as phenotypical female with primary amenorrhea, breast development and no pubic hair at adolescence. Mild clitoromegaly depends on AR

insensitivity; if inguinal hernia is present strongly suspect AIS.

CAIS management has two important aspects. First to facilitate patients for functional vagina for sexual relationship and secondly the risk of malignancy with cryptorchid testes. The first line management for neovagina is progressive vaginal dilatation. The patient's motivation and willingness to use dilators regularly is the key to success. The Vaginoplasty may be considered depending on patient's choice and the size of the vagina in specialist centres after discussion with multidisciplinary teams [52]. In CAIS cases the uterus, fallopian tubes, ovaries, cervix and upper one third of vagina are absent. The progressive regular use of vaginal dilators can give good results for achieving a reasonable size vagina suitable for coitus. The main aim is to attain puberty. It is better to delay gonadectomy until after puberty [55]. The smooth pubertal growth with endogenous hormones can be achieved and secondly tumour development in CAIS is very rare before puberty [55, 53, 52]. CAIS is the only exception to remove gonads in the presence of Y chromosome after puberty though with regular surveillance during pubertal growth [56]. AMH is high in CAIS cases where source is testicular Sertoli cells [57].

The diagnosis of an XY karyotype in female phenotype at adolescence is difficult for the patient and family to accept. It may cause psychological and emotional stress with fear of undermining gender identity. The discussion should be based on facts with very sensitive and empathetic approach towards patients as well as parents. They should be offered psychological counselling, introduction to support groups, online educational resources for example androgen insensitivity syndrome support group and www.dsdfamilies.org.

Ovarian disorder

Gonadal dysgenesis results in defective or incomplete development of the gonads, usually due to structural and numerical disturbance of chromosomes. The majority of women have an X chromosome abnormality, 25% may have normal 46XX karyotype with subtle abnormality on the X chromosome. Gonadal dysgenesis with 46 XX karyotype with sensory neuro deafness, known as Perrault syndrome. The commonest abnormality is Turner syndrome classically associated with 45 X0 while those with a 46 XY karyotype, known as Swyer syndrome [58].

Turner's syndrome

Turner's syndrome has a typical phenotype as webbed neck, short stature, absent sexual development, low set ears and widely spaced nipples. When the typical phenotype is missing, the usual presentation is delayed growth, primary amenorrhoea and absent secondary sexual characteristics. The hormonal profile is hypergonadotropic hypogonadism. The karyotype is diagnostic with 45 X0 in 40%-60% of cases or mosaic (45X0/46XY, 45X0/46XX) in others [59]. The incidence of Turner's syndrome is 5 in 10,000 and is the most common cause of POI in adolescence [60]. Turner's syndrome women are at increased risk of medical problems, one third have cardiovascular abnormalities including aortic and mitral value abnormalities, coarctation of the aorta, aortic aneurysm and spontaneous aortic dissection [61]. The mortality increases by threefold due to cardiac abnormalities and pregnancy further increases the morbidity and mortality [59]. The renal abnormalities include horseshoe kidney, unilateral renal agenesis, partial or complete duplication of the renal collecting system. Autoimmune thyroiditis, hepatitis, type 1 diabetes, thrombocytopenia and coeliac disease are also common with Turner's syndrome. These patients need additional surveillance and evaluation with echocardiography (ECHO) at the time of diagnosis, if normal repeat every 5 years. The renal ultrasound at diagnosis, every 3-5 years repeat if normal and more frequent monitoring in problematic cases. The blood tests including thyroid function test, full blood count, lipid profile, antiendomysial antibodies, renal and liver function tests at the time of diagnosis and repeat every 1-2 years. Audiometry at diagnosis and repeat every 10 years if normal. Attention deficit hyperactivity syndrome (ADHD) is more common in patients with Turner syndrome [61].

Mangement

Early diagnosis and initiation of treatment with growth hormone (GH) helps to achieve a reasonable height up to 150cm and puberty induction. The crucial factor for final height is the dose of GH and duration of treatment before the oestrogen. The oestrogen therapy can be delayed until 14 years of age in order to achieve the maximum growth potential [59]. In late diagnosis, the height gain with GH is limited. The treatment with a synthetic steroid hormone Oxandrolone (an anabolic steroid) shows better results for height [59]. There are reports of spontaneous pregnancies in the literature with Turner's syndrome resulting in miscarriage and associated with increased risk of sex chromosome aneuploidy. The best option for pregnancy is via egg donation [60].

Swyer syndrome

The phenotypical female appearance with 46 XY chromosomes and male gonads may present as inguinal hernia(s). The non-functional gonads are like streaks and do not produce AMH nor androgens. This condition is also known as complete gonadal dysgenesis. The vagina, cervix, uterus and fallopian tubes develop normally but external genitalia fail to masculinise [54]. The prevalence of 46XY gonadal dysgenesis is 1.5/100,000 case [54]. The usual presentation is delayed secondary sexual characteristics and primary amenorrhoea. The gonadectomy is recommended as soon the diagnosis is confirmed to eliminate the risk of malignancy in cryptorchid testes.

Ovarian dysgenesis with 46 XX karyotype

The phenotype is a normal female and there are no obvious somatic abnormalities, presents with delayed puberty [62]. The FSH and LH receptor gene mutations and gonadotropin resistance leads to cessation of oestrogen production from the ovaries. The enzymatic deficiencies and autosomal genes role to block the steroidogenesis from both ovaries and adrenals.

Perrault syndrome

The sensorineural hearing loss with ovarian dysgenesis and 46 XX karyotype, known as Perrault syndrome. The presentation is usually in childhood and ovarian dysfunction ranges from gonadal dysgenesis, primary amenorrhoea to POI with progressive ovarian follicular dysgenesis due to gene mutations [63]. The patients usually have learning disabilities, delayed development, cerebellar ataxia, sensory

and motor neuropathies [63]. The management involves hearing aids, cochlear implants, puberty induction and maintenance of bone mineral density. Fertility options include egg donation, egg preservation in cases where POI is suspected [64].

Premature ovarian insufficiency (POI)

POI is hypergonadotrophic hypogonadism before the age of 40 years and varies hugely in cause and phenotype. The majority of cases present with secondary amenorrhoea, may present before the menarche. The risk of POI with primary amenorrhea is 10-28% while 4-18% with secondary amenorrhoea [65]. In POI, the ovaries resemble menopausal ovaries. The prevalence of POI differs in ethnic groups, more prevalent in Caucasian's and African Americans compared to Chinese and Japanese women [66]. Structural and numerical chromosomal abnormalities, fragile X chromosome, autoimmune disorders and exposure to radiation and chemotherapy, infiltrative and infectious process and even pelvic surgery may impair ovarian function.

Galactosaemia (a rare autosomal recessive disorder) can precipitate POI where pathophysiology involves rapid follicular atresia due to cumulative toxicity of galactose metabolites in germ cells [68]. All women with POI should be offered screening for Fragile X mental retardation (FMR1) gene testing and discussion about the possibility of transmission to off spring [8].

There is a strong association between autoimmune adrenal and ovarian insufficiency – therefore screening for anti-adrenal antibodies in women with POI is recommended [69]. There is no place for ovarian biopsy for diagnosis. The tests for 21 hydroxylase enzymes, if positive, then further evaluation of adrenal function is required. The negative cases require regular surveillance for 21 hydroxylase enzyme tests for early detection and treatment for adrenal problems [69]. Autoimmune thyroiditis is relatively more common in POI [69].

The factors determining the radiotherapy damage to oocytes include, dose of radiation, exposure time and the age of the women at exposure. Abdominal radiation can cause myometrial, cervical and endometrial abnormalities due to the disturbance of muscular architecture [70]. The cranio-pharyngeal radiation affects the HPO axis, results in amenorrhoea and anovulation, extra pelvic radiation has no real risk of permanent damage to ovaries especially with pelvic shielding. The transposition of ovaries, urgent oocytes, embryos or ovarian tissue cryopreservation should be explored and offer before the pelvic radiations. The options depend on patients' choice and the availability of the service. There is no evidence of increased birth defects in babies where mothers are treated with radiations, chemotherapy, or both [71]. The chemotherapeutic agents attack the actively dividing cells and results in reduction of primordial follicles. The effect is type of medication and dose dependent though advanced age, and multiple drug therapy is more hazardous. The long-acting GnRH down regulation of ovaries to create hypo gonadal state before treatment is also an option. The women treated with GnRHa develop irreversible POI in less than 10% cases while 40%-70% receiving the same therapy without GnRHa [72].

Out of 10-20 women with POI, one can have, spontaneous pregnancy [73].There should be detailed discussion about contraception where fertility is not desired. The diagnosis of POI can be emotionally upsetting to the patient and family. They should be supported with evidence-based information for future fertility like donor oocyte for pregnancy, hormone replacement and regular monitoring for BMD and appropriate psychological counselling. In cases of POI before puberty induction of puberty is similar to those with hypogonadotropic hypogonadism cases.

Eugonadotropic hyperandrogenism

Hyperandrogenism with normal gonadotropins can present with primary amenorrhoea. The symptoms of premature adrenarche are severe acne, hirsutism, alopecia (male baldness), clitoromegaly, deepening of voice. In these cases, total free serum testosterone, Dihydroepiendrostenidione (DHEAS), Androstenedione, 17 OH progesterone should be requested to exclude reasons for excess androgen production. Total free serum testosterone between 2-5 nmol/L is usually PCOS, more than 5 nmol/L needs further evaluation to find the source of the androgen production [2]. Raised 17 OH progesterone needs further evaluation via ACTH stimulation test to rule out congenital hyperplasia (CAH).

Polycystic ovary syndrome (PCOS)

The PCOS is a diagnosis of exclusion and is the commonest condition with mild hyperandrogenism. The agreed diagnostic criteria for adult PCOS, known as Rotterdam criteria and features,

1. Ultrasound appearance of ovaries >10-12 follicles <10mm in size in the periphery of ovary or volume of ovary more than $10cm^3$.
2. Biochemical (raised serum free testosterone, raised LH/FSH ratio, low or normal SHBG).
3. Oligomenorrhoea, hirsutism, acne and male pattern baldness, the presence of two out of three features helps to establish the diagnosis [74].

The prevalence of POCS is 6%-18% in adolescent girls [75]. The usual presentation is oligomenorrhoea or secondary amenorrhoea and rarely primary amenorrhoea. PCOS with primary amenorrhoea has severe metabolic disturbances like raised testosterone, dyslipidaemia and acanthosis nigricans, increased risk of depression and anxiety compared to PCOS with secondary amenorrhoea [76, 77].

In adolescence the Rotaderm criteria overlaps with normal pubertal growth and makes the diagnosis biased and confrontational [78, 79]. The World Health Organisation defines adolescence as age between 10 and 19 years with symbolic changes in growth and pubertal development. The International evidence-based guidelines for PCOS assessment and management in adolescence helps to avoid under and over diagnosis of PCOS [79]. The features considered for the diagnosis are oligomenorrhoea as per years after menarche as the cycles are usually irregular during the first 3 years post menarche and hyperandrogenism features or raised assays [79]. The menstrual cycle is longer than 90 days for one or more years post menarche or ranges from 21 to 45 days after 1-3 years or less than 21days or more than 35 days after 3 years of menarche or primary amenorrhoea by 15 years of age or more than 3 years post thelarche is considered as abnormal menstruation [79]. Hyperandrogenism presents as hirsutism, acne or biochemical results confirmed by assays. The pelvic ultrasound scan and AMH are not the diagnostic criteria for

PCOS in adolescence. In cases where features are only suggestive of PCOS, not diagnostic, regular surveillance is recommended with symptomatic treatment. The ultrasound for ovaries after 8 years of menarche can help in making the diagnosis where symptoms persist. It is important to observe and exclude eating disorders and other psychological symptoms [80]. The management involves, healthy life style interventions e.g. weight management and symptomatic treatment. The combined oral contraceptive (COC) pill or metformin or together are useful. Though metformin is unlicensed in UK for PCOS, it helps to regulate hormonal imbalance and in turn helps to regulate menstrual cycle and reduction in acne and hirsutism in selected cases [81, 82]. In young lean girl's metformin 850mg daily dose is usually enough wile in overweight adolescent higher doses in the range on 1.5gm-2.5 gm is used [81]. The COC reduces the circulating free androgens by lowering the production from ovaries and increase in sex hormone binding globulins. The antiandrogens like cyproterone acetate and flutamide stop the peripheral conversion of testosterone into potent Dihydrotestosterone have role for severe acne and hirsutism for short period of time [81].

Adult-onset congenital adrenal hyperplasia (CAH)

The CAH due to 21 hydroxylase deficiency is the most common form. It presents in adolescence or in adulthood. The usual symptoms are primary amenorrhoea or oligomenorrhoea, early pubarche, severe acne, hirsutism or clitoromegaly [83]. It is a common autosomal recessive condition with prevalence of 1:1000 and more common in certain ethnicity groups like Ashkenazi Jews [84]. Early morning follicular phase17 hydroxyprogesterone (17-OHP) level more than 6 nmol/L is suggestive of CAH. An ACTH stimulation test will confirm the diagnosis in cases with 17 OHP levels between 2 nmol/L-6 nmol/L. In primary amenorrhoea with CAH, treatment with hydrocortisone helps to alleviate the excessive androgen levels.

The raised androgens could be due to hyperandrogenism like Cushing's syndrome, glucocorticoid resistance, androgen secreting adrenal and ovarian tumours [54]. The high serum DHEA-S or androstenedione, suspect androgen producing adrenal tumours. Rarely these are ovarian in origin [85]. The ACTH and CRH release from neuroendocrine tumours can result in over production of cortisol from the adrenals, results in hyperandrogenism. Glucocorticoids used in high doses can also cause Cushing's syndrome [86]. A 24 hours urinary free cortisol, midnight salivary cortisol or 1mg dexamethasone suppression test (Oral administration of 1 mg Dexamethasone at midnight and check serum cortisol at 0800 hrs in the morning) to rule out Cushing's syndrome after this screening do diagnostic tests to find the cause [86]. The Dexamethasone-CRH test is performed by giving 0.5mg of dexamethasone every 6 hours for 48 hours total of eight doses and check serum cortisol after 15 minutes of CRH 1µg/kg body weight, which is given two hours after the last dexamethasone dose. The serum cortisol less than 1.4 µg/dL rule out Cushing's syndrome.

Ambiguous genitalia

In cases of ambiguous genitalia chromosomal karyotyping is performed early in infancy. The 46 XY karyotype with 5 α reductase deficiency where testosterone cannot be converted into dihydrotestosterone (DHT) which is necessary for external genitalia masculinisation. The external genitalia are more like female genitalia.

Incomplete androgen insensitivity (IAIS) presents with varying degree of androgen signalling and babies may have ambiguous genitalia at birth. In some indistinct cases at puberty scanty pubic hair along with breast development and clitoromegaly is the usual presentation [87]. In cases of IAIS gonadectomy should be considered early to remove gonads to avoid unwanted virilisation at puberty [57]. In cases of IAIS appearance is usually phenotypical female and external genital appearance may vary according to androgen exposure, they may be raised as a girl or a boy depends on the response of androgens [52].

In cases with 46XX karyotype the cause is CAH in 95% of cases due to 21 hydroxylase deficiency and excess of androgens masculinise the external genitalia [88]. Placental aromatase deficiency is a rare cause which results in too much androgen exposure to the fetus and results in ambiguous genitalia and sometimes maternal signs of severe acne, hirsutism in pregnancy [89].

The management is multidisciplinary involving parents and family in the decision-making and gender assignment. It is very sensitive and difficult time for the parents and they need thorough counselling, emotional and psychological support. Each case should be assessed individually and parents should be involved in each step from diagnosis to the management [90]. These children need regular follow up, hormonal support and reassurance for wellbeing, an experienced surgeon should perform the gonadectomy or surgery to genitalia if required.

Induction and maintenance of puberty

The puberty induction to achieve breast and uterus development, growth spurt for height and bone mass expected for their age is cornerstone. The normal ovarian function begins around 11 years of age, so low dose oestrogen is added at 11-12 years of age for hypo and hypergonadotropic females. The start can be delayed if treatment of an underlying cause like cancer or waiting to achieve height with GH. The goal of therapy is to resemble normal pubertal milestones. Oestrogen should be commenced at a low dose (0.25-0.5 mg) preferably via transdermal route and be natural 17 β-oestradiol instead of synthetic preparations (Donaldson *et al* 2019). The dose of oestrogen is adjusted for body weight or fixed increments for every 3-6 months with regular Tanner staging review to assess the response to treatment [91, 92]. It is important to adjust the dose of oestrogen to achieve appropriate height. The progestin is added after two or two and a half years of unopposed oestrogen or when breakthrough bleeding starts or when the endometrium is ready on ultrasound scan usually more than 7-8 mm. Progestin use for 10 days every 1-3 months protects against endometrial hyperplasia and irregular bleeding. The treatment should continue in cases with an established diagnosis till the average age of menopause (age 51-52). The duration can be tailored according to the risk assessment individually for hormone replacement.

Summary

The presentation of primary amenorrhoea in adolescence is associated with emotional, psychological and physical problems. An early diagnosis, hormone replacement if required and psychological support is mandatory as part of the management plan. The approach is via a

multidisciplinary team in the presence of adolescent gynaecologist and paediatric endocrinologist. The treatment of underlying cause and oestrogen replacement for promoting normal sexual development is essential. Each case should be assessed individually and genetic testing helps in cases with CHH, CAIS and POI, but routine autosomal genetic testing is not required. Decisions for gonadectomy and surgery needs thorough counselling of patients and parents to help them make an informed decision. In central HP axis problems reproductive outcome is usually reassuring. In POI case, timely diagnosis can facilitate fertility preservation in some situations.

Author contributions

All authors contributing for the preparation of this review. The first literature search and draft were prepared by A.Khan with the help of K.Younas. All figure and tables by A.Khan. K.younas cross checked literature search and helped with draft preparation. E. Kevelihan did the final proof reading and helped with final submission.

Conflicts of interest

All authors have no conflict of interest to declare.

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