Management of a girl with delayed puberty and elevated gonadotropins

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Abstract

A girl presenting with delayed puberty and elevated gonadotropins may have a range of conditions such as Turner Syndrome (TS), Primary Ovarian Insufficiency (POI) and 46,XY DSD. An organized and measured approach to investigation can help reach a timely diagnosis. Management of young people often requires specialist multidisciplinary input to address the endocrine and non-endocrine features of these complex conditions, as well as the psychological challenges posed by their diagnosis. Next generation sequencing within the research setting has revealed several genetic causes of POI and 46,XY DSD which may further facilitate an individualized approach to care of these young people in the future. Pubertal induction is required in many and the timing of this may need to be balanced with other issues specific to the condition (e.g., allowing time for information-sharing in 46,XY DSD, optimizing growth in TS). Shared decision-making and sign-posting to relevant support groups from the outset can help empower young people and their families to manage these conditions. We describe three clinical vignettes of girls presenting with delayed puberty and hypergonadotropic amenorrhea and discuss their clinical management in the context of current literature and guidelines.

Keywords: Turner syndrome, primary ovarian insufficiency, 46,XY DSD, ovary development, primary amenorrhea, delayed puberty, estrogen, support groups

Introduction

Girls with delayed puberty and absent periods can present to a wide range of health professionals. Endocrinologists frequently play a central role in establishing an appropriate diagnosis and management plan. Primary amenorrhea is defined as an absence of periods after 15 years of age in girls with a degree of breast development or after 13 years of age in those with complete absence of pubertal signs. Delayed puberty is often self-limiting, but occasionally it is the presenting feature of a wide range of underlying conditions, many of which have life-long management implications. With this in mind, engaging the young person in a sensitive manner and gaining their confidence from the outset is extremely important.

The initial consultation with the young person and appropriate family members needs to include a careful history to establish key features of the presentation and any past medical and family history that may provide insight into an underlying diagnosis. Any examination should be performed sensitively, with the young person's consent and understanding of why it is necessary and with a chaperone present as appropriate. Assessment should be made of weight and height in relation to mid-parental height and pubertal stage, pubertal development using Tanner stages, the presence of any potentially relevant associated features such as virilization, and blood pressure. Dignity should be maintained and invasive examination avoided. Virilizing conditions are rare and can be assessed by external genital examination for clitoromegaly if suspected. If an intimate examination is required, then it is not essential that this takes place on the first visit and it can be postponed until a relationship with the clinical team has developed [1].

For this review, we focus on the girl with *absent (delayed) puberty* and *elevated gonadotropins* (hypergonadotropic amenorrhea), and use three case scenarios to highlight key points specific to the individual diagnoses, followed by a discussion on management considerations that are related to conditions presenting with hypergonadotropic hypogonadism. Figure 1 illustrates how this scenario fits in with other causes of primary amenorrhea.

Case 1 – Turner Syndrome

A 14 year-old girl presented with short stature, primary amenorrhea and delayed puberty. Her height was on the 3rd centile (mid-parental height 75th centile) and weight on the 10th centile. Pubertal staging demonstrated Tanner breast stage 2 with no signs of virilization. There was a history of early feeding difficulties and otitis media up to the age of five but no current reported hearing loss. Parents were non-consanguineous and there were no difficulties at school, although she was feeling increasingly isolated from friendship groups because of her delayed puberty.

Blood pressure was normal for height. Investigations showed normal thyroid function, LH 25 IU/L, FSH 62 IU/L, and *AMH 0.5 pmol/L. A karyotype showed 45,X, consistent with Turner Syndrome. Transabdominal ultrasound revealed a small, prepubertal uterus and very small, 0.2cm^3 ovaries bilaterally with no follicle activity. Bone age was delayed (11 years 8 months). Subsequent investigations included an echocardiogram that showed a tricuspid aortic valve and normal dimensions of the ascending aorta. A renal ultrasound was normal. Other recommended screening tests were unremarkable other than a formal hearing test which revealed mild conductive hearing loss. Treatment was started with growth hormone and titrated up to achieve an insulin-like growth factor 1 (IGF-1) within the high-normal range. Pubertal induction was commenced using one fourth of a 25 mcg 17β estradiol patch changed twice weekly. Contact was made with a Turner Syndrome support group as well as psychology services within the endocrine multidisciplinary team. Fertility expectations with pregnancy using oocyte donation was discussed shortly after diagnosis.*

Turner syndrome (TS) affects 1 in 2500 girls and women and results from complete or partial loss of one X chromosome. Karyotypes associated with Turner syndrome include monosomy X (45,X), 45,X mosaicism (45,X/46,XX, mosaicism with Triple X, or 45,X/46XY), isochromosome Xq, and ring X chromosome. The phenotype of TS is variable and can present at different stages in life but classically TS is characterized by POI and extra-gonadal features, including short stature, hypothyroidism, and cardiac defects such as coarctation of the aorta. POI in TS tends to be early-onset (50-85%), presenting with delayed puberty, primary amenorrhea, and hypergonadotropic hypogonadism. Turner syndrome is thought to account for 10% of females presenting with primary amenorrhea. However, the reproductive phenotype of TS can vary, with

approximately 30% of girls with TS having spontaneous thelarche, 15% presenting with secondary amenorrhea and a further 3-5% having ongoing spontaneous menstrual cycles and even achieving spontaneous pregnancies [2–4]. The mechanisms underlying this variability is not clear, although X chromosome dosage likely plays a role: mosaic TS is associated with an increased rate of spontaneous pubertal development and fertility [5,6]. Alternative explanations include altered X inactivation patterns, haploinsufficiency of pseudoautosomal region genes, or genomic variability in key X-chromosome genes modifying the reproductive phenotype of TS [7,8].

The presence of Y chromosome material, i.e., 45,X mosaicism involving an Y cell line, on karyotype or FISH analysis represents a particular challenge as it confers a risk of gonadoblastoma in approximately 10% of these individuals [9]. Prophylactic gonadectomy is recommended in all individuals with TS who have detectable Y chromosome material [9].

There are clear international consensus guidelines on how best to diagnose and manage TS [9]. These cover genetic testing, growth, puberty, fertility counselling, cardiovascular health, and health surveillance for comorbidities such as hearing impairment, diabetes, and dyslipidemia. This presentation of an adolescent with TS raises several issues. There may be relief or frustration that past medical issues are now explained by the diagnosis of TS. Input from a psychologist may include liaison with the school for educational review and support needs. Specific to this age group is the conflict between promoting growth with growth hormone and ensuring timely pubertal progression with exogeneous oestrogen [10]. Estrogen at high doses has the potential to accelerate closure of the long bone epiphyses, compromising growth and raising the question of whether pubertal induction should be delayed for a period to allow growth hormone take effect. Earlier studies found that relatively high doses of estrogen compromised final adult height and advocated for a delay in oestrogen introduction [11]. Later trials, however, demonstrated that low dose oestrogen used in tandem with growth hormone at or after the age of 12 did not have a significant impact on final height [12–14]. Pubertal induction, and specific considerations in girls with TS, are discussed below.

Case 2 – Primary Ovarian Insufficiency

A 14 year-old girl presented to her primary care doctor due to concern that puberty had not yet started. She was otherwise completely well and excelled academically. A maternal aunt had autoimmune hypothyroidism but there was no other relevant family history. Her parents were first cousins and she had two brothers who had entered puberty at an expected age. Her mother had her menarche at 12 years old, had no difficulty conceiving, and was not menopausal at the age of 50. Pubertal staging revealed no breast development (B1), sparse pubic hair (P2) and no axillary hair (A1). Height and weight were on the 50th centile with a mid-parental height on the 75th centile. Examination was otherwise normal. Investigations revealed positive thyroid peroxidase (TPO) antibodies, markedly raised gonadotropins (LH 42 IU/L; FSH 96IU/L), and an undetectable serum estradiol concentration.

Further testing at a reproductive medicine unit two months later demonstrated similar gonadotropin concentrations, a 46,XX karyotype, weakly positive TPO antibodies, negative adrenal (ACA/21OH) antibodies, normal thyroid function, and a negative Fragile X screen. A diagnosis of Primary Ovarian Insufficiency (POI) was confirmed. Puberty was gradually induced with 17β estradiol transdermal patches (see Pubertal Induction). This girl was devastated by the diagnosis of POI and developed depression requiring medication. She benefitted from clinical psychology input and from a POI support group. She was frustrated by the lack of explanation for her condition and joined a research study looking at genetic causes of POI. Trio exome sequencing revealed a pathogenic homozygous variant within STAG3, *a gene required for normal human meiosis that has been previously associated with POI.*

POI arises from an inherent defect within the ovary that results in estrogen deficiency and infertility secondary to depletion of the follicle pool [15,16]. POI affects 1% of females and rarely can be early-onset, presenting in adolescence with primary amenorrhea, early secondary amenorrhea, or delayed/arrested puberty. POI is diagnosed in those presenting before the age of 40 years with raised FSH (>25IU/L) on two occasions at

least a month apart; biochemical estrogen deficiency; and amenorrhea for a least four months [17,18]. AMH measurement and ovarian ultrasound are of limited diagnostic use in POI and are not routinely indicated clinically [17].

Several causes of POI have been identified. Iatrogenic causes, such as chemotherapy, radiotherapy, and surgery, explain up to 30% of POI diagnoses in some clinical populations [19,20]. This is likely to rise as survivorship of pediatric cancer continues to improve. Autoimmune mechanisms have also been implicated in the pathogenesis of POI in up to 30% of women [21–23], and autoimmune conditions in general are more frequent in women with POI . Common autoimmune associations include hypothyroidism, autoimmune polyglandular syndrome, Addison's disease, celiac disease, and pernicious anemia [21]. Anti-ovarian antibodies can be positive in varying proportions of women with POI (4-69%), but the role of these antibodies in the pathogenesis of POI is unclear [24]. Current European Society of Human Reproduction and Embryology (ESHRE) guidelines suggest that measuring anti-TPO, adrenocortical, and 21-hydroxylase antibodies can be considered at diagnosis if the clinical picture suggests an autoimmune etiology; if positive, these antibodies can be useful markers of autoimmunity in women with POI [17].

There is also a significant genetic component to the pathogenesis of POI, supported by the high incidence of familial POI (up to 30%) particularly within consanguineous families [25] and the association of POI with several syndromes (see *Table 1).* The most common associated clinical features are short stature (Turner syndrome) and deafness (Perrault syndrome). Taking a careful family history and performing a systematic clinical examination at the time of presentation is important. X chromosome abnormalities as well as copy number variants of key X chromosome region genes (*DACH2, XPNPEP2, POF1B, DIAPH2*), are a recognised cause of POI in 2-5% of women with this condition. *FMR1* premutations, associated with Fragile X, accounts for approximately 3% of women with POI but rarely presents with primary amenorrhea [29]. In recent years, next generation sequencing approaches within a research context have identified a variant possibly contributing to a POI diagnosis in up to 50% of women within these studies [30–36]. However, the functional evidence for the pathogenicity of these variants varies.

Establishing causality is further hindered by small pedigrees and a remarkably heterogeneous genetic architecture; variants in over 100 genes have been implicated in the pathogenesis of POI with several postulated modes of inheritance including oligenic and polygenic inheritance patterns. *Table 2* outlines genes within which pathogenic variants have been clearly demonstrated to cause POI in humans. Over recent years these variants have highlighted the importance of developmental processes such as oogenesis and meiosis to normal ovarian function. Abnormalities within genetic mechanisms required for meiosis have emerged in recent years as a significant underlying cause of POI [67]. Meiosis is a complex series of events beginning in fetal life, when homologous chromosomes form the synaptonemal complex. *STAG3* encodes for one of the cohesion proteins that stabilize this complex. Meiotic homologous recombination follows, a process for which DNA repair is essential. Accordingly, pathogenic variants in DNA repair genes (e.g., *BRCA2, MSH4, MSH5, MCM8, MCM9, ZSWIM7)* are amongst those implicated in the pathogenesis of POI *(Table 2)*.

Some countries offer panel-based sequencing approaches to selected women (e.g., via the National Genomics Test Directory in the UK), but, broadly, expanded genetic testing beyond karyotyping and Fragile X screening is not currently recommended in clinical practice [17]. The diagnosis of POI remains unexplained in 50-80% of women which can be frustrating and impedes an individualized approach to management.

Case 3 – 46,XY DSD

A girl was referred just after her 15th birthday because she had not started puberty. Her parents had also had late puberty so did not worry initially. On examination, there was no breast development (B1), minimal pubic hair (P2), no signs of genital or systemic virilization, and no other notable features such as hyperpigmentation. No inguinal gonads were palpable. Her height and weight were on the 25th percentile in keeping with delayed puberty (mid-parental height 50-75th centile). Her blood pressure was normal (110/65 mmHg). Basal gonadotropins were elevated (LH 44 IU/L, FSH 77 IU/L) and electrolytes normal (sodium 140 mmol/L, potassium 4.1 mmol/L).

After discussion with the parents and young person, further tests were undertaken. The karyotype was 46,XY; a transabdominal ultrasound suggested a possible very small "Müllerian structure" and intraabdominal gonad on the right; and adrenal investigations were normal (basal cortisol, basal ACTH, co-syntropin stimulation test, urine steroid profile analysis). Basal tumor markers were negative (α-fetoprotein, β-hCG). Abdominal magnetic resonance imaging showed a small vestigial uterus and small bilateral intraabdominal streak-like gonads. A likely diagnosis of complete gonadal dysgenesis was made ("Swyer syndrome").

Further sharing of information was undertaken with specialist psychology input and multidisciplinary team discussion. It was felt that her gender identity was female and she wanted to start estrogen replacement for induction of puberty. After counseling, a clinical genetic gene panel for "DSD" was done which identified a de novo *hemizygous missense variant in the HMG-box of* SRY. *With informed consent, vaginal examination, vaginoscopy and laparoscopy was performed under anesthetic. A typical clitoris, vagina and cervix was seen, and small uterus. During the same procedure, bilateral streak-like gonads were removed, as had been discussed and consented for in advance. Cryopreservation of gametes was not felt to be an option. Histology showed a streak gonad on the left and a slightly larger severely dysgenetic gonad with well-contained gonadoblastoma on the right. Ongoing support was given and pubertal induction undertaken, which resulted in progressive uterine growth on ultrasound imaging one year later.*

The mostly likely diagnosis in a 46,XY girl presenting with absent puberty and elevated gonadotropins is complete gonadal (testicular) dysgenesis (sometimes known as Swyer syndrome) [1,68]. However, complete blocks in androgen synthesis such as Leydig Cell Hypoplasia (LHCG receptor) and complete combined 17α-hydroxylase/17,20-lyase deficiency (17αOHD) must not be overlooked, especially if LH is higher than FSH. 17αOHD is a rare form of congenital adrenal hyperplasia (CAH) associated with hypertension and hypokalemia, so checking blood pressure and serum electrolytes at

presentation in all 46,XY girls or women is important [69]. Measurements of progesterone, a urine steroid profile and ACTH-stimulation test should be performed if there is any clinical suspicion of 17αOHD or if the diagnosis is otherwise unclear, especially when testes are identified or when LH is dominant. The presence of virilization in a 46,XY girl (often with some breast development and mildly elevated gonadotropins) expands the differential diagnosis to include 17β-hydroxysteroid dehydrogenase deficiency type 3 (17βHSD), 5α-reductase deficiency type 2 (5αRD), defects in *NR5A1* (also known as SF-1) and very rarely partial gonadal dysgenesis and partial androgen insensitivity syndrome, although these latter conditions would usually be diagnosed earlier with atypical genitalia in infancy. Of note, women with complete androgen insensitivity syndrome (CAIS) usually have breast development and gonadotropins are not usually significantly elevated (especially FSH), so usually would not present with absent puberty with elevated gonadotropins (Fig. 1). A full clinical examination and consideration of associated features is warranted given that up to a fourth of infants with 46,XY DSD have an associated anomaly, and sometimes these individuals may first present in teenage years with renal issues (e.g., WT1/Frasier syndrome) [70]. Prior history is also important, such as primary adrenal insufficiency due to congenital lipoid adrenal hyperplasia (e.g., steroidogenic acute regulator protein, CYP11A1), especially if a karyotype was not done previously [71].

A transabdominal pelvic ultrasound is an essential initial investigation of 46,XY DSD and can help identify a diagnosis. Imaging is very important in order to identify and characterize any gonads present and to define uterine structures, but is often not straight forward. Although transabdominal pelvic/inguinal ultrasound is a useful initial investigation, magnetic resonance imaging can be more useful in delineating complex anatomy in teenage years. Müllerian structures are usually present on imaging in complete gonadal dysgenesis but the uterus and upper vagina are absent in conditions affecting androgen synthesis (e.g., 17αOHD, 17βHSD, 5αRD).

Importantly, 46,XY DSD conditions such as complete gonadal dysgenesis can be associated with a risk of gonadoblastoma and malignancy of up to 40%, depending on underlying diagnosis and age [72,73]. A prophylactic gonadectomy should be performed in

any child with a Y chromosome who has a streak or dysgenetic intraabdominal gonad [74]. Biomarkers (e.g., α-fetoprotein, β-HCG) may suggest gonadoblastoma but are more reliable in the context of established germ cell tumours and ultimately a diagnosis can only be made on histopathological analysis after gonadectomy. Ascertaining the correct timing and approach to gonadectomy requires informed conversations with the child, family, and involved healthcare professionals [75,76]. An additional consideration is deciding whether or not to attempt experimental cryopreservation of small gonads in selected young people. Cryopreservation will usually not be possible for 46,XY girls presenting with complete gonadal dysgenesis and elevated gonadotropins. Sometimes, the appropriateness of cryopreservation needs to be decided upon intra-operatively with prior consent in place. A new diagnosis of 46,XY DSD in children and adolescents requires that the need for age-appropriate, paced information sharing is balanced with the need to address medical issues with a degree of urgency [1].

Genetic testing in the setting of 46,XY DSD has become increasingly available with reasonable turnaround times in recent years in many countries [77]. Variants and copy number variants in many genes have been implicated in DSD pathogenesis (*SRY, NR5A1)* and the number of associated genes is increasing [78]. Overall, a diagnosis can be achieved for about 25% of individuals with complete gonadal (testicular) dysgenesis, but much higher where there is clear evidence of a steroidogenic defect [79]. Identifying a pathogenic variant can cement the diagnosis and can yield important information for the wider family; for example, variants in *NR5A1* (SF-1) be associated with a range of phenotypes within a pedigree, including POI in 46,XX girls and women [44]. Genetic testing, as always, needs to be approached with care and with appropriate counseling.

Discussion

These three clinical vignettes outline three key differential diagnoses to consider when approaching the management of a young person with absent puberty and elevated gonadotropins. Taking a full history and performing a sensitive, systematic examination can help reach a diagnosis.

A karyotype must be performed early on in the diagnostic process; the finding of a complete or partial X chromosome deletion prompts full workup for TS, and the finding of any Y chromosome material requires planning for a gonadectomy to manage tumor risk. Pelvic imaging and AMH measurement are useful when investigating 46,XY DSD, possibly helpful when considering fertility options in TS, and of no significant benefit in POI. Other investigations may be appropriate depending on the likely diagnosis. *Figure 1* shows how the presentations of primary amenorrhea discussed in this review can be approached using a diagnostic algorithm. Several issues that arise in clinical practice are not reflected by this simplified diagram. For example, breast development is not often a clear binary characteristic; limited breast development may be seen in some girls with elevated gonadotropins, especially if they are overweight. Regarding uterine imaging, a uterus that has never been exposed to oestrogen can be so small as to appear absent even to MRI scanning – a "clandestine uterus" [80,81]. In the presence of estrogen deficiency, an absent uterus can only be declared after several months of estrogen administration and repeat imaging.

The clinical scenarios discussed above highlight several important management principles when planning the care of a girl presenting with absent puberty and hypergonadotropic gonadal insufficiency. We expand on some of these further below.

Pubertal induction

Regardless of cause, young people presenting with delayed or arrested puberty require pubertal induction. Careful liaison with a pediatric endocrinologist is needed to maximise breast and uterine development using as physiological an approach as possible [82]. Studies of serum estradiol concentrations in puberty show that levels begin to rise from the age of 10 with the median age of menarche being 13 years. To mimic this physiology, induction of puberty ideally should take place at 11-12 years of age over two to three years with the dose of estradiol increasing from about 10% of the adult dose to a full physiological dose [17]. There are several pubertal induction regimens which vary by country [82–85]. A common approach in Europe is to gradually increase transdermal

estrogen patches from one fourth of a 25mcg patch worn for four days of the week, to a full patch changed twice weekly [83]. This dose can be titrated against individual variable response, assessed either by Tanner staging or by transabdominal ultrasound of the uterus, and dose adjustments departing from fixed regimen can be made accordingly [86]. The combined oral contraceptive pill (COCP) is not recommended for use in pubertal induction: it contains supraphysiological doses of synthetic estrogen which is associated with greater risks of hypertension, thrombosis, and dyslipidemia [87–89].

Progestogens should be commenced for uterine protection after at least two years of unopposed oestrogen or once breakthrough bleeding occurs [17]. The timing of the introduction of progesterone can be further guided by ultrasound assessment of endometrial thickness. The average age of presentation of primary amenorrhea is usually over the age of 14 and often as late as 18 years. In such circumstances the dose of estrogen may need to be increased at a faster pace than usual, according to individual response and preferences and considering optimal psychological benefit [90]. Pubertal induction in TS can pose specific challenges, including balancing adequate estrogen replacement with optimizing growth, as discussed above [9]. All individuals on estrogen replacement should have regular follow-up consultations to review the goals of treatment, psychosexual well-being, and hypoestrogenic symptoms.

Once pubertal induction is complete, individuals with hypergonadotropic hypogonadism require ongoing hormone replacement with estrogen and progesterone at physiological doses (HRT) until approximately the age of natural menopause. Maintenance HRT needs to be tailored to the individual patient's needs, preferences, and hypoestrogenic symptoms. HRT regimen can use cyclical progesterone with withdrawal bleeds or continuous progesterone with no bleeds. Estrogen replacement can be administered transdermally, orally, or topically; oestradiol esters and 17β oestradiol are most often used. There is no evidence that HRT confers an increased risk of breast cancer in women using lifelong estrogen replacement therapy up to the age of natural menopause [17]. Therefore, no change to standard breast cancer screening is required.

Bone health

Bone is an important target organ for estrogen, and estrogen deficiency is acknowledged to cause impaired bone mineral density (BMD) and an increased risk of fractures [91,92]. BMD should be measured at diagnosis and at 5 yearly intervals throughout life [17,93]. Supraphysiological doses of oestrogen may be considered for those with low bone density below the age of 50 years. Factors associated with a low BMD in the setting of ovarian insufficiency include low vitamin D, suboptimal calcium intake, primary amenorrhea, and low body mass index (BMI) [94–96]. The importance of bone protection in the setting of ovarian insufficiency needs to be discussed from diagnosis: optimal dietary calcium and vitamin D intake, maintaining a healthy weight, weight-bearing exercise, and not smoking [97–99].

Fertility options

Fertility options will be limited for women with hypergonadotropic gonadal insufficiency but nevertheless a full discussion of the topic is important soon after diagnosis. This discussion should be revisited at intervals throughout follow up, as the technology and opportunities in this field are evolving.

Assisted conception with donated oocytes has been used to achieve pregnancy for over 20 years and remains the main fertility treatment option for the majority of women presenting with raised gonadotropins [100]. The availability of donated oocytes varies from country to country and this option is not acceptable for some people. Adoption is also a commonly chosen route to family life. In the oncology setting, a small number of pregnancies have been achieved internationally using ovarian tissue cryopreservation approaches [101]. Despite possible discordance between gonadal type and gender identity, pregnancies from cryopreserved gonadal tissue in vitro maturation (IVM) of sperm may be possible for individuals with 46,XY DSD in the future, the latter avoiding the potential risk of reintroducing tissue carrying a malignancy risk [75]. Even when follicular apparatus

is found, fertility preservation is not usually possible for women with POI who have raised FSH. However, cascade genetic screening of family members of women with POI may allow pre-symptomatic intervention for women at risk of POI who have yet to develop it. Young women with mosaic TS and persistent ovarian function are potential candidates for oocyte cryopreservation; however, in the main, oocyte donation is the main fertility option for women with TS [9,102]. Pregnancies in TS need to be carefully monitored by an expert multidisciplinary team given the increased morbidity and mortality risks conferred by pregnancy in these women (aortic dissection, hypertension) [9,103].

Sexual function

In many countries a significant proportion of girls have sexual intercourse before the age of 18. This topic has to be approached cautiously but not neglected. If possible, an adolescent gynecologist should be available early in the young person's journey so that they can then be a familiar advisor when required. Several endocrine aspects are relevant in this area. For example, in post-pubertal girls who have reached sexual maturity, vaginal estrogen may be required for adequate vaginal lubrication and testosterone may be added later if libido is low[104].

The chances of spontaneous fertility should also be discussed, even with those presenting with primary amenorrhea: spontaneous conceptions do occur in POI and TS in approximately 1-5% of adult women with these conditions [2,3,5,105–107]. There are no corresponding data for adolescents, although their chances of conception are likely to be much lower. It is important to address the possibility of pregnancy, however remote, as contraception is required for those not desiring to conceive.

Psychological considerations

Diagnoses associated with hypergonadotropic hypogonadism can be very difficult life experiences for both the young person and parents and signposting reliable information sources is essential from the outset.

A TS diagnosis in a young person is associated with specific psychological issues, including an increased risk of anxiety, social isolation, reduced self-esteem, and shyness. These problems can manifest in school and, later, in the workplace. Support of a clinical psychologist can help deal with these issues. Most women with TS have IQs in or above the normal range; 10% have learning difficulties, especially with 45,X/46,X,r(X) karyotype, and neuropsychological review at key transition points during schooling is recommended. Timely pubertal induction and management of any hearing impairment can promote psychosocial wellbeing. Support groups can be very useful (e.g., TSSS, the Turner Syndrome Support Society UK).

A diagnosis of POI is challenging psychologically and in adults has been associated with increased risk of depression, low levels of self-esteem, and negative effects on sexuality [108,109]. It is a particularly difficult diagnosis in a young person, and access to a clinical psychologist and support groups (e.g., The Daisy Network (UK)) is helpful. Regular specialist follow-up is recommended so that young people have access to accurate and up to date fertility information and so that the need for psychology support can be reassessed at intervals. Often crises arise some years after the original diagnosis, for instance when a near relative achieves a pregnancy.

Early specialist psychological input from the time of presentation is also essential for a girl with 46,XY DSD. These young people often have delayed puberty and may be more immature than their peers, requiring graded information sharing balanced with the need to progress pressing medical issues, as discussed above. Open dialogue is paramount and the young person needs be involved with decision-making processes and feel

connected with the team; often, children can give appropriate consent or assent depending on the legal framework of the jurisdiction. Repeated assessment of gender identity is essential, especially when considering induction of puberty and other endocrine interventions. Consideration of different cultural backgrounds and preferences is also important. A DSD diagnosis can be challenging for parents and caregivers too, who have a lot to take in within a short space of time. Again, in addition to clinical psychology, there are resources for information sharing and support groups available (e.g., dsdfamilies, www.dsdteens.org).

Conclusion

A range of diagnoses, including Turner Syndrome, POI, and 46,XY DSD, may explain the presentation of delayed puberty and raised gonadotropins in a young girl. A judicious investigation plan, beginning with a karyotype, facilitates a timely diagnosis. These are rare conditions and an awareness of relevant international consensus guidelines and research developments are useful when planning and directing clinical care. Multidisciplinary input, open communication, shared decision-making, and dedicated support groups can help young people and their families.

Data availability

No original data are included in this manuscript.

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Table 1. Selected syndromic forms of POI with summary of ovarian phenotype.

Syndromic POI and clinical synopsis including ovarian phenotype	Chromosome anomaly/gene variants
Turner Syndrome and variants Short stature, web neck, renal anomalies, otitis media, bicuspid aortic valve, coarctation, hypothyroidism. NB 45,X/46,XX mosaicism associated with milder phenotype and late presentation.	Karyotype 45,X, 45,X/46,XX or 45,X/46,XY mosaicism, mosaic ring X, isodicentric Xq, and other X chromosome variants
Autoimmune polyendocrinopathy syndrome type I Mucocutaneous candidiasis, hypoparathyroidism, and Addison disease. POI affects up to 50% of females, rarely before menarche.	*AIRE* AR - Finland, Iranian Jewish community, Sardinia
Woodhouse-Sakati Syndrome POI usually presenting as primary amenorrhea followed by diabetes, hypothyroidism, alopecia, extrapyramidal movements, sensorineural hearing loss.	*DCAF17* AR – strong founder effect in Saudi Arabia and Qatar
Perrault syndrome Sensorineural deafness, short stature and POI, the majority with primary amenorrhea.	*HSD17B4, HARS2, LARS2 CLPP C10orf2, CLDN14+ SGO2, KIAA0391, ERAL1 account for 50% of cases* AR
Blepharophimosis, ptosis, epicanthus inversus syndrome (BPES) Type 1 variant associated with POI, usually secondary amenorrhea. Narrow eyelid opening and ptosis may be evident at birth.	*FOXL2* AD
Galactosemia POI (>80% of females) presents with primary (50%) or secondary amenorrhea (50%) after neonatal metabolic presentation.	*GALT* AR
Pseudohypoparathyroidism type 1a	*PHP1a*

Childhood onset hypocalcemia, high phosphate, cataracts, seizures. ~50% delayed puberty. POI caused by partial gonadotropin resistance.	AD
Ovarioleucodystrophy Early onset ataxia with white matter disease. POI with primary or secondary amenorrhea and ovarian atrophy.	*EIF2B2, EIF2B4* AR
Ataxia telangiectasia Early onset ataxia <2 years followed by telangiectasia. POI; rare pregnancies recorded.	*ATM* AR
Premature aging syndromes Scleroderma-like skin change from adolescence. POI usually as secondary amenorrhea. Diabetes mellitus in 80%. Rare pregnancies reported.	*WRN, ANTXR1* AR
Progressive external ophthalmoplegia Primary amenorrhea in ~50%. Presentation with ophthalmoplegia and ptosis but rare POI with no other features	*POLG* AR
Fanconi anaemia POI usually presents at >20 years of age. Also associated with developmental delay, short stature, cardiac defects, genitourinary and gastrointestinal abnormalities, craniofacial abnormalities, VACTERL association, radial ray abnormalities.	*FANCA, FANCM, FANCL FANCD1/BRCA2, FANCU/XRCC2* AR
Rossetti et al, 2017 [26], Huhtaniemi et al, 2018 [27] Chow et al, 2017 [28]	

POI – primary ovarian insufficiency, AD – autosomal dominant, AR – autosomal recessive

Table 2. Selected examples of genes in which pathogenic variants have been associated with non-syndromic Primary Ovarian Insufficiency (POI), grouped by the main mechanism of action.

Mechanism	*Genes*
Ovarian stimulation and function	*LHCGR*[37], *FSHR*[38], *GDF9*[39], *BMP15*[40], *FIGLA*[41]
Steroidogenic defect	*STAR*[42], *CYP17A1*[43], *CYP19A1*[43]
Ovarian development	*NR5A1*[44], *FOXL2*[45], *POLR3H*[46]
Meiosis and DNA repair	*MSH4*[47], *MSH5*[48], *HFM1*[49], *BRCA2*[50], *REC8*[33], *SMC1B*[33], *SYCE1*[51], *CPEB1*[52], *STAG3*[53], *PSMC3IP*[54], *DMC1*[55], *MCM8*[56], *MCM9*[57], *NUP107*[58], *CSB-PGBD3*[59], *SPIDR*[60], *TUBB8*[61], *MEIOB*[62], *ZSWIM7*[63], *YTHDC2*[64]
Primary germ cell maintenance	*NOBOX*[65], *SOHLH1*[66]

Figure Legend

Figure 1: Simplified flow diagram of the pathway of diagnosis of hypergonadotropic amenorrhea and related conditions presenting with primary amenorrhea. CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; MRKH, Mayer-Rokitansky-Küster-Hauser syndrome.

Figure 1