Primary amenorrhoea: investigation and treatment

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Abstract
Primary amenorrhoea is a symptom with an extensive list of underlying causes, the majority of which are rare. By definition it should present in adolescence, although some conditions diagnosed in childhood may anticipate the failure of onset of menstruation. Many causes of secondary amenorrhoea can also present with primary amenorrhoea if they arise sufficiently early.

This review addresses some of the issues that should be taken into account in the care and evaluation of the adolescent gynaecology patient and her parents, which, although increasingly recognised as a subspecialist area of interest, should be feasible to accommodate within the provision of a general gynaecology service.

A systematic, compartment-based approach will cover the commoner causes of primary amenorrhoea and recommend a pragmatic but cost-effective approach to achieving the correct diagnosis. Treatment must be directed at the specific cause but will often have wider implications for lifelong well-being, including such areas as weight management, hormone replacement, sexual health and fertility.

Keywords adolescent gynaecology; hyperprolactinaemia; hypothalamic amenorrhoea; Müllerian agenesis; ovarian failure; polycystic ovary syndrome; primary amenorrhoea

Introduction
The failure to menstruate by the age of 16 years in the presence of normal secondary sexual characteristics, or 14 years in the absence of other evidence of puberty, define primary amenorrhoea and warrant investigation. The basic physiological principles of menstrual function enable the various disorders to be compartmentalised into those related to the outflow tract (congenital malformation or receptor insensitivity), the ovary (abnormal or absent germ cells and abnormal folliculogenesis), the anterior pituitary (disrupted gonadotrophic hormone production or secretion) and the central nervous system (CNS) (disrupted hypothalamic factors affecting pituitary signalling). The commonest diagnoses are highlighted in Table 1. Overall it is estimated that endocrine disorders account for approximately 40% of the causes of primary amenorrhoea, with the remaining 60% having developmental (genetic or structural) origins. It must not be forgotten that amenorrhoea is also frequently physiological; in this age group, pregnancy must be ruled out and constitutionally delayed puberty identified as a diagnosis of exclusion.

Evaluation of the adolescent
Consultation approach
Specialists and services should recognise that adolescence is a time of great flux and transition, and the requirements of these young women are different from those of children and adults. The environment and consultation are pivotal to the doctor–patient relationship and can have profound long-term consequences on how the patient perceives her illness and how she subsequently interacts with health care providers. She will be subject to physiological, psychological, sexual, social and educational changes, during which time the parent–child relationship evolves and increasing independence develops, alongside the influence of her peer group. Adolescence is not easy for healthy teenagers and for those with medical problems it can be a minefield.

A good rapport needs to be established between the gynaecologist (and his/her multidisciplinary team) and the patient and her parent(s). The patient should be central to the consultation but she may initially prefer for her parent, usually the mother, to communicate on her behalf. Parents and patients may have

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different concerns and agendas. Cultural taboos may surround discussions of sexual development. Social or family history factors (e.g. divorce or abusive relationships) may alert carers to the adolescent’s resilience and ability to cope with her unraveling medical problem. Language barriers should be pre-empted with the use of appropriate interpreters. It can be very helpful to engineer the opportunity to talk separately and privately to both the patient and parent. A trusting relationship needs to be maintained with both patient and parent, but there may be issues of confidentiality, particularly on behalf of the patient with respect to sexual issues which, it should be emphasised to her, will remain undisclosed in joint discussion. The gynaecologist should also view the encounter as an opportunity for health education and promotion, e.g. advising on smoking cessation and safe sexual practice.

**History, examination and baseline investigation**

A thorough history should include enquiry about growth and development, seeking other signs of puberty. Evidence of psychological dysfunction or emotional stress should be borne in mind through verbal and non-verbal cues, and in relation to enquiry about the family and social (educational) history.

It is important to explain what is intended in the form of physical examination and to obtain verbal consent from the patient and parent. The patient should understand that consent may be withdrawn at any time. Examination should take place in comfort and privacy and in the presence of a professional chaperone. Relevant points are listed in Table 2.

It may be clear from the history that examination under anaesthesia will be required, in which case the adolescent should be spared the above intimate examination. Under anaesthesia, vaginoscopy may be performed with a hysteroscope or cystoscope, or the vagina may be directly inspected with a nasal speculum and a light source. It goes without saying that documentation must be meticulous and photographs taken only with appropriate consent.

Transabdominal ultrasound assessment of the pelvis is invaluable when bimanual examination is inappropriate and/or there is reason to question internal organ development and potential functional integrity.

Baseline investigations are listed in Table 3.

**Amenorrhoea of hypothalamic/CNS origin**

**Weight-related amenorrhoea**

The hypothalamus is central to the normal functioning of the reproductive axis. The transition of puberty is driven by the maturation of the gonadotrophic releasing hormone (GnRH) pulse generator and its output of gradually increasing pulse amplitude and frequency. Between the ages of 8 and 13 years, pituitary gonadotrophin release occurs, initially nocturnally and then also by day, culminating in the adult pattern of 90-min pulses. The precise mechanism driving the hypothalamus is not yet fully clear but there is a close relationship to body weight and in particular to body fat proportion. White fat produces the satiety hormone leptin, which has hypothalamic receptors. Its action is mediated through the inhibition of neuropeptide Y, which in turn reduces GnRH pulsatility. This has been interpreted as a signal from the fat stores to the brain that adequate levels of body fat have been reached for successful reproduction. The balance is then struck by reduced food intake, leading to reduced thermogenesis, increased insulin output (liberating biologically active sex steroids from insulin-like growth factor binding protein-1 and sex hormone binding globulin suppression) and increased GnRH pulsatility.

There has been some evidence that a critical fat mass of 22% is required for this sequence of events to occur. This theory explains the earlier onset of menarche observed in affluent societies over the past 100 years, and the absence of menarche in malnourished girls, particularly anorexic girls and those undertaking significant exercise (ballet dancers, gymnasts and especially competitive endurance sportswomen). Treating the problem requires the cause to be addressed, which can uncover major conflicts of psychological disturbance and distorted body image in the case of eating disorders, and may be perceived to compromise sporting or artistic success in the case of excessive exercise. The former is the realm of the psychiatrist/psychotherapist and should be addressed upon diagnosis. For the latter, sometimes a relatively minor reduction in exercise intensity and/or increased caloric intake may suffice to trigger resumption of hypothalamic activity. Delayed puberty becomes medically significant when there is a risk of poor bone mineralization and osteoporosis. Peak bone mass is achieved at age 25 years and therefore prolonged oestrogen deficiency through late adolescence is ill-advised. Some young women and their parents may prefer to wait until her competition days are over before allowing normal pubertal events to take place. Interestingly, the amount of exercise, even though it is weight-bearing, does not compensate for osteoporotic changes which have been extensively studied in dancers. If osteoporosis is a concern, puberty may be induced with gradually increasing oral oestrogen therapy (2 mcg ethinylestradiol daily, increasing by 5 mcg every 6 months to 20 mcg, then conversion to the combined oral contraceptive pill [COCP]).

| Examination of the adolescent with primary amenorrhoea |
|-------------------|-------------------|-------------------|-------------------|
| General            | Weight, height, body mass index |
|                    | Blood pressure     |
|                    | Clinical thyroid status |
|                    | Dysmorphic signs   |
| Abdomen/pelvis    | Mass arising from pelvis |
|                    | Groin nodes/heriae |
| Perineum           | Inspection is often all that is required, especially in the non-sexually active. Note presence and distribution of pubic hair, clitoral size, configuration of hymen, relationship of anus, vagina and urethra to hymen, the degree of oestrogenisation and perineal hygiene. The hymen and vestibule may be visualised with gentle lateral spread of the labia majora with two fingers and a deep inspiration/Valsalva manoeuvre by the patient |

Table 2
An interesting theory as to the hypothalamic origin of the aetiology of polycystic ovary syndrome (PCOS) has recently been put forward. It has been suggested that PCOS may be the result of the incorrect establishment of the GnRH pulse generator ‘set-point’ at puberty, such that the pituitary responds with inappropriate and excessive luteinising hormone (LH) secretion, leading to the premature arrest of ovarian follicle development, ovarian hyperandrogenism and amenorrhoea. This might come about due to earlier attainment of the critical body fat mass in an individual who has an intrinsic/genetic predisposition to insulin resistance.

Constitutionally delayed puberty is characterised by a positive family history, short stature, delayed secondary sexual characteristics and delayed epiphyseal maturation (identified by hand X-ray bone aging). Final height prognosis remains in the appropriate range for the parental centiles. Other causes should be ruled out and puberty induced as described above. Note that hypogonadotrophic hypogonadism is difficult to distinguish from constitutional delay and may only manifest on withdrawal of oestrogen support in due course.

### Chronic illness

Many types of chronic childhood illnesses may cause sufficient general debilitation as to compromise hypothalamic function by similar central mechanisms. A good history should also identify malabsorption syndromes (coeliac disease and inflammatory bowel disease) which warrant specific treatments. Childhood cancer requiring cranial irradiation invariably causes pubertal failure which should be proactively managed to optimise growth and development.

#### Baseline investigations for primary amenorrhoea

<table>
<thead>
<tr>
<th>Test and normal range</th>
<th>Interpretation</th>
<th>Further assessment</th>
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<tbody>
<tr>
<td>Urine pregnancy test negative</td>
<td>Rule out pregnancy</td>
<td>Progestogen challenge will induce menses in the presence of oestrogenised endometrium. Note that in some cases of PCOS, hyperandrogenic exposure of the endometrium may prevent shedding on progestogen withdrawal due to prior decidualisation</td>
</tr>
<tr>
<td>Ultrasound scan</td>
<td>Transabdominal route in non-sexually active to identify presence of uterus, cervix and upper vagina (rules out Müllerian agenesis), and ovaries (rules out gonadal agenesis). An endometrial stripe indicates oestrogen responsiveness (making PCOS more likely than hyperprolactinaemia which is an oestrogen-deficient state)</td>
<td>MRI or CT head scan will demonstrate hypothalamic tumours, non-functioning pituitary tumours causing hypothalamic compression and micro/macroadenomas of the pituitary</td>
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| Serum prolactin concentration (normal range <500 mU/L) | *Cause and typical prolactin level*
Stress/recent breast examination: <1000 mU/L
Hypothyroidism/PCOS: 700–2500 mU/L
Non-functioning macroadenoma: <3000 mU/L
Functioning microadenoma: 1500–4000 mU/L
Functioning macroadenoma: 5000–8000 mU/L
Levels >1500 mU/L warrant further assessment of the pituitary fossa | MRI or CT head scan will demonstrate hypothalamic tumours, non-functioning pituitary tumours causing hypothalamic compression and micro/macroadenomas of the pituitary |
| Serum TSH and T4 concentration (normal range: TSH 0.2–6.0 mU/L, free T4 12–27 nmol/L) | Raised TSH (and TRH) due to malfunctioning (low free T4) thyroid hormone feedback (usually autoimmune or inflammatory) interferes with tonic dopamine inhibition of prolactin | See text |
| Serum gonadotrophins (normal follicular FSH <10 IU/L, LH <10 IU/L, dependent on local assay) | Low levels (<2 IU/L) suggest hypothalamic failure
FSH levels >15 IU/L (outside an ovulatory surge) suggest impending ovarian failure and >40 IU/L confirm ovarian failure
When LH is concurrently elevated ovarian failure is confirmed | Clinically evaluate for anosmia and/or colour blindness which suggest Kallmann's syndrome
Karyotyping is indicated in the adolescent with apparent ovarian failure to identify Turner's syndrome and its variants
Bone density measurement is important in the oestrogen-deficient
Autoantibodies may reveal an autoimmune cause for ovarian failure
Ultrasound may have confirmed PCOS morphology.
Consider biochemical evaluation of androgens in the presence of clinical hyperandrogenism (hirsutism, severe acne) to rule out androgen-producing tumours and CAH |

TSH: thyroid stimulating hormone; free T4: free thyroxine; TRH: thyrotropin releasing hormone; FSH: follicle stimulating hormone; LH: luteinising hormone; CAH: congenital adrenal hyperplasia.
Space-occupying lesions
Space-occupying lesions of the hypothalamus (craniopharyngiomas, germinomas, gliomas, dermoid cysts) are rare but when they do occur, they tend to exhibit clinical effects around the time of puberty. They cause amenorrhoea by disrupting the tonic inhibition of dopamine on prolactin release and/or compress and destroy hypothalamic and pituitary tissue. They are likely to present with other concerning symptoms of a neurological nature (headache, visual field defects) and evidence of other pituitary hormone dysfunction, including galactorrhoea. Diagnosis will involve cranial imaging and neurological/neurosurgical input. Invariably destructive therapy in the form of surgery and/or radiotherapy is required. Subsequent hormone replacement will depend on the resulting deficiencies.

Kallmann’s syndrome
This is the rare (1:50 000) congenital absence of GnRH neurons whose cell bodies have failed to migrate from the olfactory area to the arcuate nucleus of the hypothalamus through the cribiform plate at the base of the skull, with the axons extending down the tuberoinfundibular tract to connect with the portal vasculature of the anterior pituitary gland. It may be sporadic or inherited (autosomal dominant or X-linked recessive) and is associated with anosmia and colour blindness.

Therapy
Where possible, therapy should be directed at the cause of the problem. Induction of puberty with oestrogen has been discussed and until such time as fertility is required, hormone replacement with the COCP or naturally-derived products conventionally targeted at menopausal women are entirely satisfactory in the medium to long term. The onset of breast development associated with a growth spurt rapidly solves the problem. Many young women also welcome the option of minimising menses to three to four times per year by taking COCP cycles back to back. This strategy, apart from its social convenience, also minimises periods of oestrogen deficiency which can be unpleasantly symptomatic. In isolated hypothalamic dysfunction, fertility can be restored either with GnRH administered through a subcutaneous needle and pump device, delivering physiological pulses to an intact pituitary, or with daily bolus exogenous follicle stimulating hormone (FSH) and LH by subcutaneous injection. The former is somewhat cumbersome as the pump must be worn continuously until ovulation, but has the advantage of generating unfollicular recruitment and spontaneous ovulation. Gonadotrophin ovulation induction requires careful monitoring to guard against the risk of multiple pregnancy and ovarian hyperstimulation syndrome.

Amenorrhoea of pituitary origin
Hyperprolactinaemia
Hyperprolactinaemia is the commonest pituitary cause of amenorrhoea, although it is not a common presentation in adolescents with primary amenorrhoea. It can arise due to the development of a tumour which can be a micro (<10 mm) or macro (>10 mm) adenoma, of the functioning or non-functioning variety, either by the cells intrinsically over-producing prolactin or the mass effect disrupting the tonic inhibition exerted by hypothalamic dopamine. When amenorrhoea is the consequence of hyperprolactinaemia, presenting symptoms are more commonly related to oestrogen deficiency. Up to 30% may have galactorrhoea but this bears no correlation with prolactin levels or the presence of a tumour. Only 5% will display visual field defects. Persistently elevated prolactin (>1500 mU/L) associated with amenorrhoea warrants pituitary imaging. Magnetic resonance imaging does not incur radiation hazards and is more sensitive than computed tomography but takes longer and is more expensive. Typical changes include asymmetrical enlargement of the pituitary fossa with a double contour to its floor and erosion of the clinoid processes. Suprasellar extension risks compression of the optic chiasm and invasion of the cavernous sinuses.

Therapy: A more conservative approach to management is evolving. Dopamine-agonist treatment is favoured for prolactin-secreting tumours displaying rapid growth or those that are large at diagnosis. Bromocriptine is started at a dose of 1.25 mg per night for 5 nights, and is gradually titrated up to 7.5 mg daily in two or three divided doses over about 3 weeks. Common side-effects include nausea, vomiting, headache and postural hypotension, and are minimised by initiating therapy at night and then taking tablets with food. Longer-term adverse effects include Raynaud’s syndrome, constipation and psychiatric changes, especially aggression, which can occur at the start of therapy. Carbergoline (0.25–1 mg twice-weekly up to 1 mg daily) is longer acting and better tolerated by many patients who experience unacceptable side-effects on bromocriptine. However, it also can have psychiatric side-effects and therefore should remain second-line. Surgery (transsphenoidal resection of the adenoma) is reserved for those with intolerable side-effects to medication, non-functioning macroadenomas or suprasellar extension that has not resolved with medical therapy. Pituitary irradiation is seldom required with the availability of modern neurosurgical skills, and is associated with a significant risk of subsequent medium/long-term panhypopituitarism that warrants lengthy surveillance. Hypopituitarism can also occur post-operatively but it is immediately apparent.

Asymptomatic, incidentally-detected microadenomas of the pituitary are common (up to 10% of the population). They rarely grow, and if they do, progress is slow. They should be imaged at 1, 2 and 5 years and if there has been no change, no further follow-up is required.

Iatrogenic causes of hyperprolactinaemia include the use of dopaminergic antagonist drugs such as antipsychotic phenothiazines, domperidone and metoclopramide. If it is not possible to alter the culprit medication, oestrogen deficiency problems can be remedied with the COCP. Serum prolactin concentrations should be monitored to ensure they do not rise further, suggesting another cause, e.g. adenoma.

Empty sella syndrome
This is a benign condition arising due to congenital absence of the sellar diaphragm. Extension of the subarachnoid space into the pituitary fossa flattens the pituitary separating it from the hypothalamus. It can also occur following surgery, radiotherapy or the development of a tumour. It does not progress to pituitary failure although its usual manifestation is hyperprolactinaemia. In this case, therapy is as described above, with surveillance for a few years to exclude the development of an adenoma.
Amenorrhea of ovarian origin

Premature ovarian failure

Unlike the testes, ovaries devoid of gametes are unable to produce normal amounts of steroid hormones, leading to elevated concentrations of serum gonadotrophins. Several chromosomal abnormalities result in gonadal dysgenesis, the commonest being 45XO or Turner’s syndrome. Others include Turner’s mosaics and XY mosaics (Swyer’s syndrome). Any primordial oocytes reaching the gonads undergo accelerated and premature attrition. Most girls with Turner’s syndrome are diagnosed in the neonatal period or in infancy due to phenotypic abnormalities. All will experience primary amenorrhea and should undergo artificial induction of puberty in conjunction with specialised optimisation of growth through the care of the paediatric endocrinologist. Some with a mosaic karyotype will begin to go through puberty but fail to menstruate, or may suffer early secondary amenorrhea. Any evidence of Y chromosomal material warrants surgical excision of the gonads to remove any risk of malignant change (gonadoblastoma) within them. During adolescence the gynaecologist has a role in the multidisciplinary care of girls with Turner’s syndrome to optimise pubertal development in respect of appropriate body image and also to promote uterine growth in anticipation of potential pregnancy achieved in due course through oocyte donation and intravenous fertilisation (IVF) techniques. Until that time, cyclical menses may be achieved with the COCP or hormone replacement as previously described.

Premature ovarian failure (POF) may also result from polyglandular autoimmune syndromes (in conjunction with combinations of hypothyroidism, hypoparathyroidism, hypoadrenalism/Addison’s disease and type 1 diabetes). It can be difficult to detect ovarian autoantibodies due to the poor sensitivity of current assays.

An increasingly common cause of POF in adolescence is childhood cancer that has required gonadotoxic chemotherapy (e.g. alkylating agents like cyclophosphamide) and/or pelvic irradiation (e.g. Hodgkin’s disease or Wilms’ tumour).

Resistant ovary syndrome

Rarely, the ovary may contain a normal complement of primordial follicles yet fail to respond to the gonadotrophin stimulus. Most cases remain unexplained, although rare mutations of the FSH receptor have been identified in some, and earlier growth factors in primordial follicle recruitment have been implicated by others.

The same advice applies with respect to the induction and support of puberty and menstrual function, and counselling with respect to fertility prospects with donated oocytes.

Polycystic ovary syndrome

PCOS is the commonest endocrinopathy to affect women of reproductive age and is also one of the commonest causes of primary (and secondary) amenorrhea. Gonadotrophin concentrations are normal/low normal and oestrogen concentrations satisfactory. An underlying hypothalamic abnormality of increased GnRH pulsatility has been suggested to contribute to the pathogenesis of the condition. PCOS is frequently associated with clinical or biochemical evidence of hyperandrogenism and/or obesity. Indeed according to the most recent international consensus definition (Rotterdam ESHRE/ASRM Workshop, 2003), two to three criteria of (oligo-)amenorrhea, hyperandrogenism, or polycystic ovary morphology (after the exclusion of other causes of hyperandrogenism, e.g. late onset congenital adrenal hyperplasia [CAH], Cushing’s syndrome and androgen-producing tumours) suffice to make the PCOS diagnosis.

Therapy: The management of PCOS in adolescence is the subject of intense debate. There is no doubt that active management of lifestyle issues aimed at normalising body weight should be paramount and the gynaecologist has great responsibility in educating the adolescent patient and her mother in this respect. Weight gain permits the condition to manifest more severely, and sets up a ‘slippery slope’ towards worsening insulin resistance which has profound implications for life-long health (especially type 2 diabetes) and fertility. There is also accumulating evidence linking adolescent PCOS with poorer quality of life scores, especially in the overweight with severe acne. Weight loss of just 5–10% is often sufficient to shift metabolically active visceral fat and restore normal menstrual regularity. Good diet and increased exercise should continue to be encouraged until a normal weight for height is achieved. Amenorrhea may be overcome during the weight loss programme (and in the lean adolescent with PCOS) by inducing regular withdrawal bleeds either with progesterogens (e.g. medroxyprogesterone acetate 10 mg daily for 5 days every 3 months) or a COCP with a non-androgenic progestogen, antiandrogen (e.g. cyproterone acetate) or the newly marketed spironolactone derivative drosperinone. This is important to prevent endometrial accumulation and the risk of hyperplasia. Clinical hyperandrogenism is often best managed cosmetically, but some find benefit in the topical preparation Vaniqa for unsightly facial hair. If ovulation has not been spontaneously restored by the time fertility becomes important, the common sequence of therapies entails ovulation induction with clomifene citrate (with/without metformin), followed if unsuccessful by daily gonadotrophins. Ultimately IVF techniques may be employed with good success but increased risk of complications in the form of ovarian hyperstimulation syndrome.

Amenorrhea due to outflow tract abnormalities

Abnormalities of the uterus or outflow tract are rare causes of amenorrhea overall but are relatively commoner causes of primary amenorrhea. Congenital abnormalities can arise from embryological failure of canalisation or complete lack of development of the Müllerian duct, or due to the correct regression of Müllerian structures but the evolution of the female phenotype due to androgen insensitivity syndrome (46XY).

Müllerian abnormalities

Complete Müllerian agenesis is the second commonest cause of primary amenorrhea (10%) after gonadal dysgenesis (40%). Also known as Mayer–Rokitansky–Kuster–Hauser syndrome, or Rokitansky syndrome for short, it occurs in approximately 1:5000 pregnancies. The vagina is absent or hypoplastic. The uterus is usually absent although there may be a small non-communicating rudimentary remnant or anlagen, which may or may not contain endometrium. There are frequently concurrent abnormalities of the urological tract (e.g. unilateral renal agenesis, pelvic kidney,
horseshoe kidney, hydronephrosis, ureteric duplication). Ovarian development and function is normal.

Other anatomical defects include imperforate hymen, which is relatively common (1:1000), and transverse vaginal septum, which is very rare (1:80,000). In these two instances, and if there is any functional endometrium in Rokitansky syndrome, presentation is likely to include cyclical pain and ultimately the development of painful haematocolpos, haematometra and haemoperitoneum.

**Therapy**

In all cases, surgery is required to establish patency of the tract or to remove the rudimentary structure if it has no prospect of ever functioning normally. Without surgery, proximal menstrual build-up may cause serious damage to a potentially functional reproductive system. In the interim between diagnosis and surgery, menses may be suppressed with GnRH analogue therapy. Cruciate incision of an imperforate hymen is straightforward and does not require subsequent dilatation. Transverse septa can arise at different levels in the vagina and may be quite thick. Anastomosis with the upper tract is complex and should only be undertaken in tertiary centres with access to multidisciplinary specialist input from plastic surgeons. Aftercare requires the careful supported use of vaginal dilators to maintain the patency created. Rokitansky syndrome rarely requires surgery as good functional vaginal length can be established through the appropriate use of vaginal dilators over 6–12 months, and instruction on satisfactory lubrication. Psychological support is vital through this process and also in enabling the young woman to come to terms with her inability to bear her own child. Ovarian integrity means that IVF surrogacy is very successful in bringing about the birth of a genetic child in due course, with a surrogate carrying the pregnancy following embryo transfer.

**Androgen insensitivity syndrome**

Androgen insensitivity syndrome (AIS) is rare (1:60,000) but represents 5% those presenting in adolescence with primary amenorrhoea. The karyotype is 46XY with a female phenotype. The gonads are testes which exhibit failure of spermatogenesis but maintain testosterone production. Normal secretion of testicular Müllerian inhibitory factor in utero leads to regression of internal Müllerian structures. The gonads may be abdominally located or in the inguinal canals. Pubic and axillary hair are absent. The labia minora tend to be juvenile and the vagina is short and blind-ending. Breast development occurs due to peripheral aromatisation of testosterone to oestrogen.

**Therapy**

There is a risk of malignant change in the malpositioned gonads but this is rare prior to the completion of puberty, and it is generally felt that endogenous hormone production produces a smoother pubertal transition and more normal early breast development. They may be removed by an appropriately skilled laparoscopic surgeon on completion of the growth spurt. Hormone replacement must follow to complete breast development, and to maintain bone health and general well-being until the natural age of the menopause. Vaginal dilatation may be required to generate a functional vagina as in Rokitansky syndrome. Sadly these young women are unable to conceive by any of the assisted reproductive technologies and coming to terms with this profound news requires specialist counselling support.

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**FURTHER READING**


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**Practice points**

- Adolescent gynaecology patients require specialist and dedicated services incorporating psychological support for diagnoses impacting substantially on body image, gender identity and fertility

- Assessment and investigation of primary amenorrhoea should be swift and comprehensive to reach the correct diagnosis and instigate appropriate therapy/give reassurance quickly with minimal disruption to family/school routine

- The commonest causes of primary amenorrhoea are: in the presence of breast development—Müllerian agenesis and AIS; in the absence of breast development with high FSH—idiopathic POI, Turner’s syndrome; in the absence of breast development with low FSH—constitutionally delayed puberty, PCOS, stress/low weight/anorexia, hyperprolactinaemia

- Most causes are chronic problems which will require patient and parental understanding of the implications for medium and long-term health and follow-up. There is an increasing number of patient support groups and specialist sources of professional and patient information which may be accessed through the British Society of Paediatric and Adolescent Gynaecology ([www.britspag.org.uk](http://www.britspag.org.uk))