

# Selected topics in **WOMEN'S HEALTH**



Laboratory investigation of  
amenorrhoea  
Polycystic ovary syndrome  
An overview of dysfunctional  
uterine bleeding  
Perimenopause and menopause  
Sexual dysfunction - loss of libido

## Amenorrhoea

Amenorrhoea is the absence of menstruation flow. It can be classified as either primary or secondary,<sup>1</sup> relative to menarche:

- **Primary amenorrhoea:** absence of menses by age 16 years in a female with appropriate development of secondary sexual characteristics; or absence of menses by age 13 years and no other pubertal maturation<sup>2</sup>
- **Secondary amenorrhoea:** lack of menses in a previously menstruating, non-pregnant female, for greater than six months<sup>2</sup>

## Primary amenorrhoea

### Key messages:

- The most common cause of primary amenorrhoea in a female with no secondary sexual characteristics is a constitutional delay in growth and puberty. In the first instance, watchful waiting is the most appropriate course.
- For females with primary amenorrhoea but who have secondary sexual characteristics, pelvic ultrasound is indicated.

### Evaluation of primary amenorrhoea

Causes of primary amenorrhoea should be evaluated in the context of the presence or absence of secondary sexual characteristics.<sup>2</sup>

#### Absence of secondary sexual characteristics

The most common cause of primary amenorrhoea in a female with no secondary sexual characteristics is hypogonadotropic (i.e. low LH and FSH) hypogonadism, often due to a constitutional delay in growth and puberty. A detailed family history may reveal a familial aspect to this. If there is a positive family history, watchful waiting is appropriate in the first instance, although the time will depend upon the age of the patient at presentation.

Testing LH and FSH is unhelpful in determining constitutional delay of puberty as low levels can be due to a delay but also a number of other conditions (Figure 1).

### Causes of primary amenorrhoea<sup>2</sup>

- **Hypergonadotropic hypogonadism/primary hypogonadism/gonadal failure:**
  - Abnormal sex chromosomes e.g. Turner syndrome
  - Normal sex chromosomes e.g. premature ovarian failure
- **Hypogonadotropic hypogonadism/secondary hypogonadism:**
  - In many cases this may be due to a familial delay in puberty and growth. Other causes include congenital abnormalities e.g. isolated GnRH deficiency, acquired lesions, endocrine disturbance, tumour, systemic illness or eating disorder.
- **Eugonadism:**
  - Anatomic e.g. congenital absence of the uterus and vagina, intersex disorders or inappropriate endocrine feedback mechanisms

In a large case series of primary amenorrhoea, the most common aetiologies were:<sup>2</sup>

- Chromosomal abnormalities causing gonadal dysgenesis (ovarian failure due to the premature depletion of all oocytes and follicles) – 50%
- Hypothalamic hypogonadism including functional hypothalamic amenorrhoea – 20%
- Absence of the uterus, cervix and/or vagina, Müllerian agenesis – 15%
- Transverse vaginal septum or imperforate hymen – 5%
- Pituitary disease – 5%

Primary amenorrhoea in females with no secondary sexual characteristics may also be caused by hypergonadotropic (i.e. high LH and FSH) hypogonadism. This is usually caused by premature ovarian failure, or gonadal dysgenesis – the most common form of female gonadal dysgenesis is Turner syndrome (45X0 karyotype).

### Presence of secondary sexual characteristics

It is recommended that a female aged 16 years or over with secondary sexual characteristics, presenting with primary amenorrhoea, is referred for a pelvic ultrasound to determine if the uterus is present. Absence of the uterus may be the result of androgen insensitivity syndrome,

where a person has a female external appearance despite a 46XY karyotype and undescended testes. It can also be due to Müllerian agenesis which is a congenital malformation characterised by a failure of the Müllerian ducts to develop, resulting in a missing uterus and variable malformations of the vagina.

If the uterus is normal, outflow tract obstruction should be considered. An imperforate hymen or a transverse vaginal septum can cause outflow obstruction. This is most often associated with cyclic lower abdominal pain from blood accumulation in the uterus and vagina. If there is no evidence of outflow obstruction, investigate as for secondary amenorrhoea (Table 1).

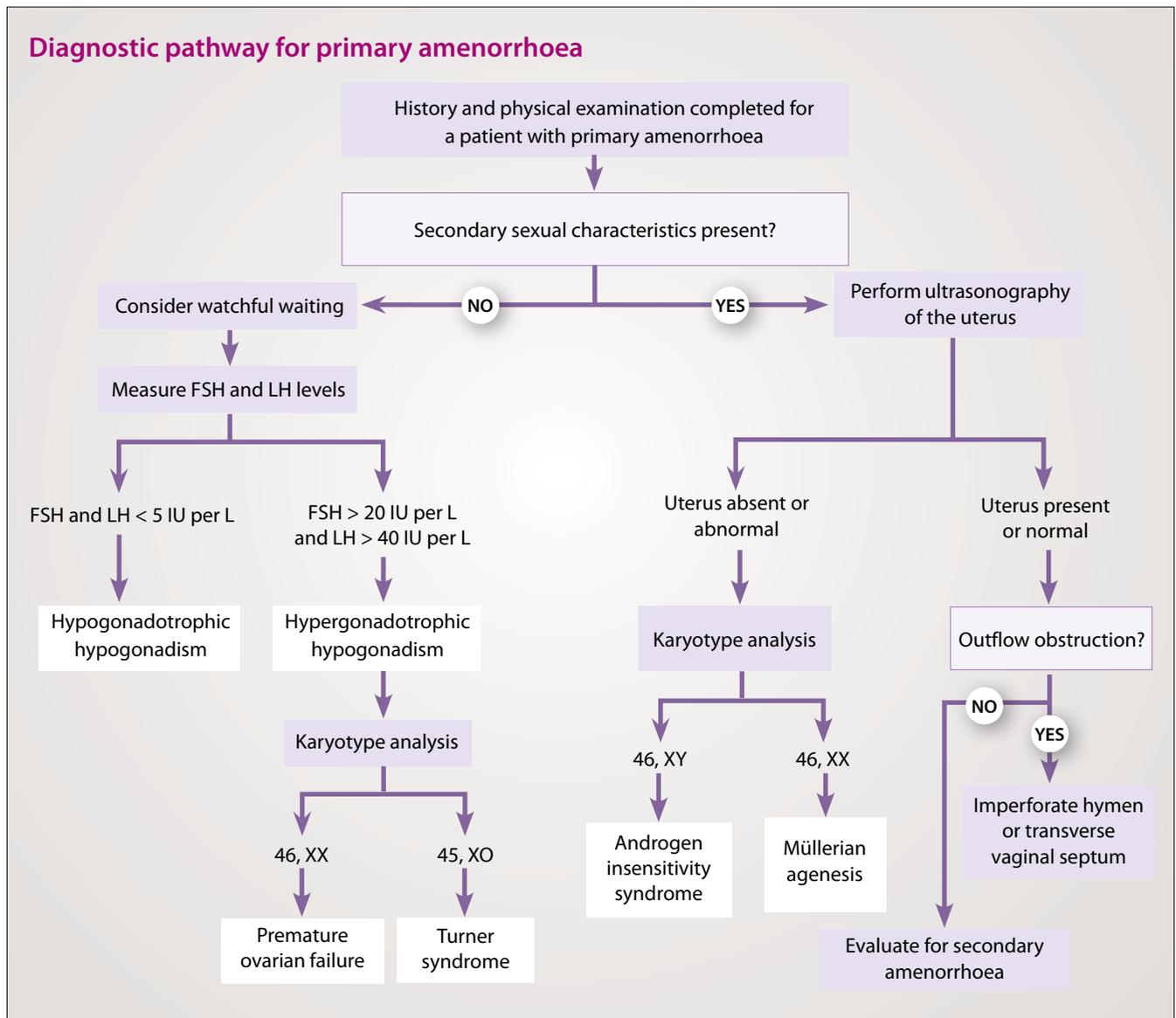


Figure 1: Investigations for primary amenorrhoea (adapted from Master-Hunter, 2006)<sup>3</sup>

## Secondary amenorrhoea

Secondary amenorrhoea is defined as a lack of menses for six months in a non-pregnant patient who was previously menstruating.

Key messages:

- Exclude pregnancy as it is the most common cause of secondary amenorrhoea
- Other than pregnancy, most cases of secondary amenorrhoea are caused by menopause, polycystic ovary syndrome (PCOS) or functional anovulation e.g. excessive exercise, eating disorder, stress or certain medicines
- FSH, TSH and prolactin measurements will help identify most causes of secondary amenorrhoea. If there is suspicion of pituitary disease, FT4 should also be tested.

### Diagnostic evaluation of secondary amenorrhoea

Pregnancy should be first excluded by either urine pregnancy test or a serum hCG, rather than relying solely on history.

The history, physical examination and measurement of FSH, TSH and prolactin will help identify the most common causes of amenorrhoea. In addition, for women with evidence of hyperandrogenism e.g. assessment of hirsutism and acne, and measurement of testosterone would also be indicated.

Results can often be difficult to interpret (Table 1) therefore review or advice from a relevant specialist may be appropriate.

### Causes of secondary amenorrhoea

After excluding pregnancy (and breast feeding), the most common causes of secondary amenorrhoea are:<sup>4,5</sup>

- Ovarian disease (40%) – ovarian failure due to normal or early menopause, hyperandrogenism e.g. PCOS, testosterone supplementation
- Functional hypothalamic anovulation (35%) – due to excessive exercise, eating disorders, stress or some medicines e.g. oral contraceptives, depot medroxyprogesterone
- Pituitary disease (19%) – has a similar presentation to functional hypothalamic amenorrhoea except for the occasional additional finding of galactorrhoea in some women. Rare causes are sellar masses, other disease of the pituitary and primary hypothyroidism.
- Uterine disease (5%) – Asherman’s syndrome is the only uterine cause of secondary amenorrhoea. This syndrome results from acquired scarring of the endometrial lining, usually secondary to postpartum hemorrhage or endometrial infection following instrumental procedure such as a dilatation and curettage.

**Table 1:** Laboratory findings in common causes of secondary amenorrhoea<sup>6</sup>

Condition	FSH	Prolactin	Testosterone
<b>Hyperprolactinaemia</b>	Normal/low	High	Normal
<b>Polycystic Ovary Syndrome</b>	Normal	Normal/slightly increased in 5–30%	Normal/moderately increased Free androgen index increased
<b>Ovarian failure</b>	High	Normal	Normal
<b>Hypothalamic</b> e.g. weight loss, excessive exercise, or stress	Low/normal	Normal	Normal

# Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is reported to affect between 5–10% of women of reproductive age.<sup>2,3</sup>

As well as taking a full history, examination of a woman with suspected PCOS should include an assessment of:

- Weight (both BMI and hip/waist ratio)
- Acne and hirsutism
- Blood pressure

## Diagnostic criteria have been developed for PCOS

PCOS is a syndrome, so there is no single diagnostic test. There are several definitions of PCOS, but generally PCOS is defined by the presence of hyperandrogenism (clinical or biochemical), ovarian dysfunction (oligo-anovulation or polycystic ovaries), and the exclusion of related disorders.<sup>7</sup> Table 2 compares diagnostic criteria for PCOS.

## Investigation of PCOS

A clinical or biochemical finding of increased androgen levels along with either menstrual abnormalities or

polycystic ovaries on ultrasound will satisfy the current diagnostic criteria (Table 2). Other tests that should be considered when investigating PCOS include FSH, TSH and prolactin levels.

Once the diagnosis of PCOS is established, fasting glucose and lipids are recommended. For women with fasting glucose >5.5 mmol/L an oral glucose tolerance test (OGTT) is indicated. In addition, some clinicians recommend that OGTT should be done for all women with PCOS who have a BMI > 30 and for all women aged over 40 years even if of normal weight.

 For more information about investigating PCOS see “Understanding polycystic ovary syndrome” BPJ 12, April 2008.

### Limited role of LH/FSH ratio<sup>8</sup>

In the past, the diagnosis of PCOS was often based upon the finding of an elevated ratio of LH to FSH in serum. Women with PCOS tend to have elevated LH concentrations, with normal to low FSH. However, while some clinicians still test LH and FSH, this is not required for a diagnosis of PCOS.

**Table 2:** Diagnostic criteria for PCOS

NIH criteria (1990)	Rotterdam Criteria (2003)	AES Criteria (2006)
<p>All three of the following:</p> <ul style="list-style-type: none"> <li>■ Clinical or biochemical evidence of hyperandrogenism</li> <li>■ Oligomenorrhoea and/or anovulation</li> <li>■ Exclusion of other disorders</li> </ul>	<p>At least two of the following:</p> <ul style="list-style-type: none"> <li>■ Oligomenorrhoea and/or anovulation</li> <li>■ Clinical or biochemical signs of hyperandrogenism</li> <li>■ Polycystic ovaries</li> </ul> <p>PCOS can be diagnosed only after the exclusion of related disorders (e.g. severe insulin resistance, androgen-secreting neoplasms, Cushing’s syndrome, hyperprolactinaemia and thyroid abnormalities)</p>	<p>All three of the following:</p> <ul style="list-style-type: none"> <li>■ Hyperandrogenism (clinical or biochemical)</li> <li>■ Ovarian dysfunction (oligomenorrhoea or anovulation and/or polycystic ovarian morphology)</li> <li>■ Exclusion of other androgen excess or related disorders</li> </ul> <p>PCOS is predominantly a disorder of androgen excess</p>

The NIH Criteria were developed first and therefore are most commonly used. The Rotterdam criteria expanded the NIH definition. The AES reviewed all available data and recommended an evidence-based definition.

NIH = National Institutes of Health, Rotterdam = European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine, AES = Androgen Excess Society

## An overview of dysfunctional uterine bleeding

Any uterine bleeding which is outside the normal menstrual patterns can be termed as dysfunctional uterine bleeding.<sup>9</sup> It can be caused by a wide variety of local and systemic diseases or related to medicines e.g. hormonal contraceptives. However, most cases of dysfunctional uterine bleeding are related to anovulatory cycles, menopause, pregnancy, structural uterine pathology e.g. fibroids, polyps or adenomyosis or a disorder of haemostasis or neoplasia. Trauma and infection are less common causes.

### Laboratory studies for dysfunctional uterine bleeding

Investigations depend on individual presentation and examination.<sup>12</sup> In many cases, it will be appropriate to first exclude pregnancy and cervical or uterine cancer as causes of uterine bleeding.

A pregnancy test is indicated for women of reproductive age with dysfunctional uterine bleeding, to exclude intrauterine or ectopic pregnancy, or gestational trophoblastic disease (hydatiform mole).

Any malignancy of the genital tract can cause dysfunctional bleeding. It can be difficult to determine whether bleeding is from an endocervical or endometrial source, so cervical cancer must be excluded. Any visible cervical lesion should be biopsied, even if cervical cytology is negative for malignancy.

Depending upon the history, clinical exam and initial evaluations, a second tier of laboratory testing may be appropriate. This may include:

- **Ultrasound examination and hysteroscopy** – useful for further evaluating women whose findings on pelvic examination are uncertain
- **TSH** – In women with signs and symptoms of hypo or hyper-thyroidism
- **Coagulation tests** – only in women with history suggestive of haemostatic defect e.g. frequent nosebleeds, easy bruising
- **Complete blood count (CBC)** – in women with evidence of anaemia

### Terminology for dysfunctional uterine bleeding

There are a number of terms used to define abnormal frequency, duration or volume of uterine bleeding.<sup>10</sup>

**Menorrhagia** — prolonged (greater than seven days) or excessive (> 80 mL daily) uterine bleeding occurring at regular intervals

**Oligomenorrhoea** — regular bleeding that occurs at an interval greater than 35 days

**Polymenorrhoea** — regular bleeding that occurs at an interval less than 24 days

**Metrorrhagia** and **menometrorrhagia** – metrorrhagia refers to light bleeding at irregular intervals. Menometrorrhagia refers to heavy bleeding at irregular intervals

**Intermenstrual bleeding** — bleeding that occurs between menses or between expected hormone withdrawal bleeds in women using hormonal contraception or postmenopausal hormone therapy

**Premenstrual spotting** — light bleeding preceding regular menses

**Post menopausal bleeding** — recurrence of bleeding or spotting in a menopausal women at least six months to one year after cessation of cycles

**Postcoital bleeding** — vaginal bleeding or spotting that is noted within 24 hours of vaginal intercourse

- **Chlamydia/gonorrhoea** – if cervicitis, vaginal discharge and/or pelvic tenderness
- **Prolactin** – useful in women complaining of oligomenorrhoea, particularly with galactorrhoea

## Perimenopause and menopause

The average woman begins menopause at approximately age 50 years. It is a retrospective diagnosis made following the cessation of menses for 12 months or more. The menopausal transition begins with variations in menstrual cycle length and ends with the final menstrual period. The perimenopausal period ends one year after the final menstrual period.<sup>11,12</sup>

Although hormone levels change throughout the menopausal period, hormone measurements are not useful for predicting the stage of the transition, or the date of the final menstrual period. FSH levels can vary significantly across cycles, so the use of FSH for predicting menopause in individual women is limited.<sup>11,12</sup>

In women aged over 45 years with symptoms suggestive of menopausal transition e.g. irregular menstrual cycles and menopausal symptoms such as hot flushes, sleep disturbance, vaginal dryness or joint and muscle aches, no laboratory testing is required.<sup>11,12</sup>

In women aged under 45 years with symptoms suggestive of menopausal transition, consider the following investigations: initially exclude pregnancy, if negative consider possible PCOS and measure prolactin, TSH, FSH levels and testosterone.<sup>11,12</sup>

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## Sexual dysfunction – loss of libido

Loss of libido has been reported to affect up to 40% of women at some time in their life.<sup>13</sup>

A full history and clinical examination, including sexual history and relationship factors is important. A key requirement for the evaluation of female sexual dysfunction is to determine whether sexual issues are associated with personal stress.<sup>13</sup>

The presence of any serious medical condition is likely to impair sexual function not only because of the condition itself, but also due to the associated impact on psychological well-being. In addition, poor self-assessed health is often associated with sexual problems.<sup>13</sup>

### Laboratory evaluation of sexual dysfunction

Laboratory testing should be performed only if indicated by history or examination.

Except in limited specialist settings, androgen levels are not helpful when evaluating the cause of a sexual problem. The correlation between androgen levels and sexual dysfunction is considered weak, apart from a few well defined situations such as proven pituitary or adrenal insufficiency or past bilateral oophorectomy. Similarly, testing oestradiol or other hormones e.g. FSH and prolactin, has limited utility in evaluating sexual dysfunction.<sup>13</sup>



**ACKNOWLEDGEMENT:** Thank you to **Dr Anna Fenton**, Endocrinologist, The Oxford Clinic, Christchurch for expert guidance in developing this article.

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