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OBG 514

REPRODUCTIVE ENDOCRINOLOGY AND FERTILITY

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Course code: OBG 514

Course title: Reproductive Endocrinology and Fertility

Course credit load: 2 Units

Series 1: Menstrual Cycle and Disorders

- **Part 1.1: The Normal Menstrual Cycle**
    - Sub Part 1.1.1: Hormonal regulation of the menstrual cycle
    - Sub Part 1.1.2: The ovarian cycle
    - Sub Part 1.1.3: The endometrial cycle
- **Part 1.2: Menorrhagia and Dysmenorrhoea**
    - Sub Part 1.2.1: Menorrhagia: definition, causes, and evaluation
    - Sub Part 1.2.2: Management of menorrhagia
    - Sub Part 1.2.3: Dysmenorrhoea: primary and secondary
- **Part 1.3: Galactorrhoea and Hirsutism**
    - Sub Part 1.3.1: Galactorrhoea: causes and evaluation
    - Sub Part 1.3.2: Hirsutism: definition and causes
    - Sub Part 1.3.3: Polycystic ovarian syndrome
- **Part 1.4: Abnormal Uterine Bleeding Patterns**
    - Sub Part 1.4.1: Intermenstrual bleeding
    - Sub Part 1.4.2: Postcoital bleeding
    - Sub Part 1.4.3: Postmenopausal bleeding

Introduction

Picture a woman confused and worried after months of unpredictable, heavy periods that have begun to interfere with her work and family life. Understanding her experience begins with a genuinely solid grasp of the normal menstrual cycle itself, the elegant hormonal choreography between hypothalamus, pituitary, and ovary that most women experience monthly without a second thought, before we can properly understand what happens when this cycle goes wrong. This Series lays that essential foundation for the whole of this course on reproductive endocrinology and fertility.

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The aim of this Series is to equip you with a thorough understanding of the normal menstrual cycle, and the disorders of menorrhagia, dysmenorrhoea, galactorrhoea, hirsutism, polycystic ovarian syndrome, and abnormal uterine bleeding patterns.

We shall commence this Series by examining the normal menstrual cycle, its hormonal regulation and the parallel ovarian and endometrial cycles. Next, we will consider menorrhagia and dysmenorrhoea. Following that, our attention turns to galactorrhoea, hirsutism, and polycystic ovarian syndrome. Finally, we will conclude by examining intermenstrual, postcoital, and postmenopausal bleeding.

Series Learning Outcomes

Upon completing this Series, you should be able to:

- **SLO 1.1:** describe the hormonal regulation of the menstrual cycle,
- **SLO 1.2:** describe the ovarian and endometrial cycles,
- **SLO 1.3:** define menorrhagia and describe its causes and evaluation,
- **SLO 1.4:** describe the management of menorrhagia and dysmenorrhoea,
- **SLO 1.5:** describe galactorrhoea and its evaluation,
- **SLO 1.6:** describe hirsutism and polycystic ovarian syndrome,
- **SLO 1.7:** describe the causes and evaluation of intermenstrual and postcoital bleeding, and
- **SLO 1.8:** describe the causes and evaluation of postmenopausal bleeding.

1.1 The Normal Menstrual Cycle

1.1.1 Hormonal regulation of the menstrual cycle

The menstrual cycle is regulated by the hypothalamic-pituitary-ovarian axis, beginning with pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, stimulating the anterior pituitary to release follicle-stimulating hormone (FSH) and luteinising hormone (LH), which act on the ovary to drive follicular development, ovulation, and, subsequently, corpus luteum formation and function.

A negative and, at one specific point, positive feedback relationship exists between ovarian hormones and the hypothalamic-pituitary axis, with rising oestrogen from the dominant follicle initially exerting negative feedback, then, once a critical threshold is sustained, switching to positive feedback, triggering the LH surge responsible for ovulation, a genuinely elegant

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physiological mechanism ensuring the precise, coordinated timing central to normal cyclical ovarian function.

Fill in the blank: The menstrual cycle is regulated by pulsatile secretion of gonadotropin-releasing hormone from the _____. A sustained rise in oestrogen switches from negative to positive feedback, triggering the LH _____ responsible for ovulation.

1.1.2 The ovarian cycle

The ovarian cycle comprises the follicular phase (during which a cohort of ovarian follicles begins development, with typically a single dominant follicle emerging under the influence of FSH), ovulation (release of the mature oocyte, triggered by the LH surge, typically occurring around day 14 of a standard 28-day cycle), and the luteal phase (during which the ruptured follicle transforms into the corpus luteum, secreting progesterone to support the early luteal phase and, should pregnancy occur, the earliest stages of implantation).

The luteal phase is characteristically more consistent in duration, typically around 14 days, than the follicular phase, which can vary considerably in length between individual women and between cycles, meaning variation in overall cycle length predominantly reflects variation in the duration of the follicular phase rather than the luteal phase itself.

Fill in the blank: Ovulation, release of the mature oocyte, is triggered by the LH surge, typically occurring around day _____ of a standard 28-day cycle. The luteal phase is characteristically more consistent in duration than the _____ phase.

1.1.3 The endometrial cycle

The endometrial cycle runs in parallel with, and is driven by, the ovarian cycle, comprising the proliferative phase (endometrial growth under the influence of rising oestrogen from the developing follicle), the secretory phase (further endometrial maturation and glandular secretory activity under the influence of progesterone from the corpus luteum, preparing the endometrium for potential implantation), and, in the absence of pregnancy, menstruation itself.

Menstruation results from the abrupt withdrawal of progesterone (and, to a lesser extent, oestrogen) as the corpus luteum regresses in the absence of pregnancy, triggering vasoconstriction of the spiral arteries, endometrial ischaemia, and shedding of the functional endometrial layer, with this entire, remarkably precisely coordinated process then repeating with the onset of the subsequent cycle.

Fill in the blank: The endometrial cycle comprises the proliferative phase, the secretory phase, and, in the absence of pregnancy, _____. Menstruation results from the abrupt withdrawal of progesterone as the corpus luteum _____ in the absence of pregnancy.

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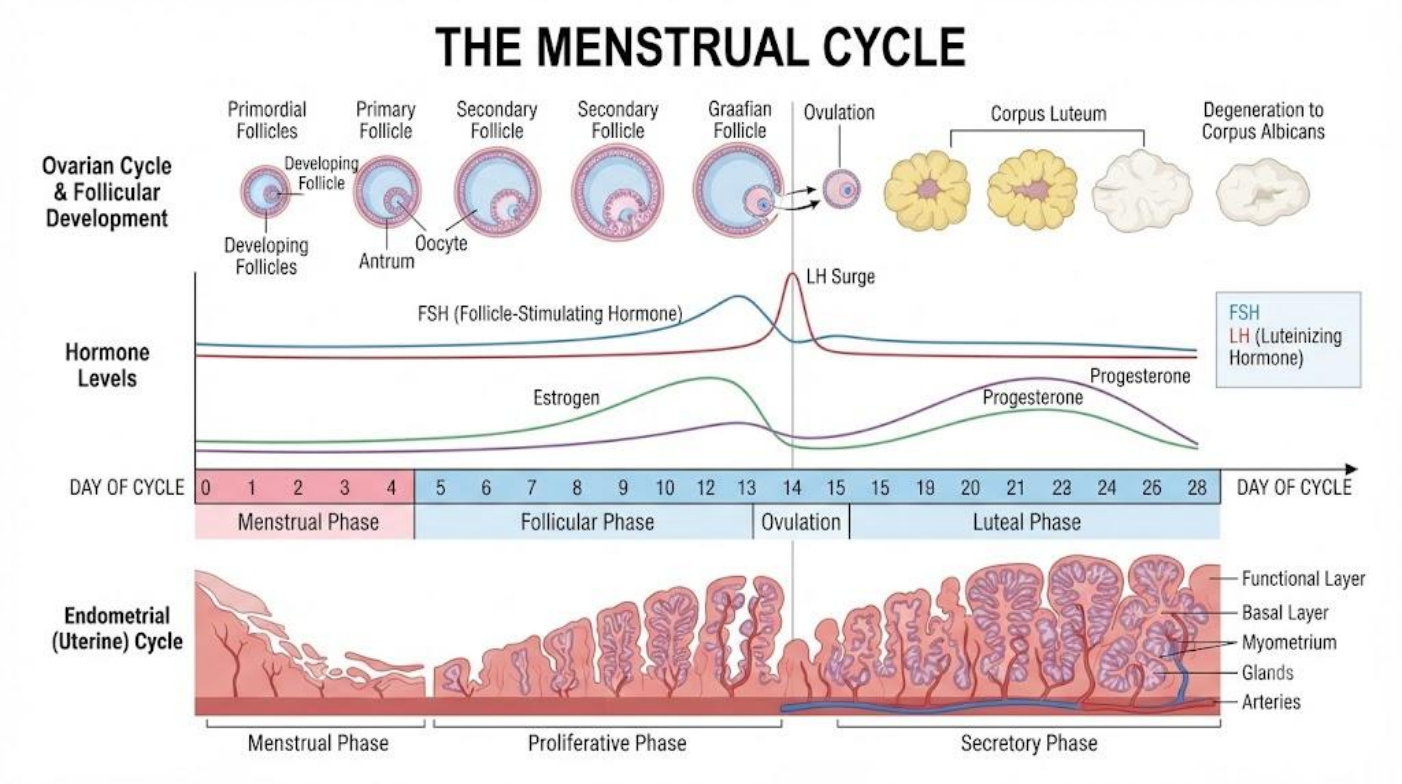

Figure 1.1: The menstrual cycle, showing parallel ovarian and endometrial phases with hormonal changes.

Pilot questions 1.1

1. Describe the hormonal regulation of the menstrual cycle by the hypothalamic-pituitary-ovarian axis. (Linked to SLO 1.1)
2. Explain the switch from negative to positive feedback triggering the LH surge. (Linked to SLO 1.1)
3. Describe the phases of the ovarian cycle. (Linked to SLO 1.2)
4. Explain why variation in cycle length predominantly reflects the follicular rather than luteal phase. (Linked to SLO 1.2)
5. Describe the phases of the endometrial cycle and the mechanism of menstruation. (Linked to SLO 1.2)

1.2 Menorrhagia and Dysmenorrhoea

1.2.1 Menorrhagia: definition, causes, and evaluation

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Menorrhagia (heavy menstrual bleeding) describes excessive menstrual blood loss that interferes with a woman's physical, social, emotional, or material quality of life, a genuinely practical, patient-centred definition now generally preferred over historical, precise volumetric thresholds that proved genuinely difficult to apply reliably in routine clinical practice.

Causes of menorrhagia include structural causes (uterine fibroids, endometrial polyps, and, less commonly, adenomyosis or malignancy), non-structural causes (ovulatory dysfunction, coagulopathy, and endometrial causes such as disordered local haemostatic mechanisms), and, in a genuinely significant proportion of cases, no specific structural or systemic cause identified, formally classified using the internationally recognised PALM-COEIN system.

Fill in the blank: Menorrhagia describes excessive menstrual blood loss that interferes with a woman's physical, social, emotional, or _____ quality of life. Causes of menorrhagia are formally classified using the internationally recognised _____ system.

1.2.2 Management of menorrhagia

Evaluation of menorrhagia includes a detailed menstrual history, examination, and, where indicated, transvaginal ultrasound to identify structural causes such as fibroids or polyps, full blood count to assess for associated anaemia, and, in selected cases, endometrial sampling, particularly in women over 45 or with risk factors for endometrial pathology.

Management of menorrhagia ranges from medical treatment (the levonorgestrel-releasing intrauterine system as first-line in many guidelines, alongside tranexamic acid, non-steroidal anti-inflammatory drugs, and combined hormonal contraception) to surgical options (endometrial ablation or, for definitive treatment or where fertility is not desired, hysterectomy), with the specific approach genuinely individualised according to the underlying cause, severity, and the woman's own preferences, including any wish to preserve fertility.

Fill in the blank: The levonorgestrel-releasing intrauterine system is first-line medical treatment for menorrhagia in many _____. Surgical options for menorrhagia include endometrial ablation or, for definitive treatment, _____.

1.2.3 Dysmenorrhoea: primary and secondary

Primary dysmenorrhoea describes painful menstruation without underlying pelvic pathology, reflecting excessive endometrial prostaglandin production driving painful uterine contraction, typically beginning shortly after menarche, and generally responding well to non-steroidal anti-inflammatory drugs, which act by inhibiting prostaglandin synthesis, or combined hormonal contraception.

Secondary dysmenorrhoea describes painful menstruation resulting from an identifiable underlying pelvic pathology, most commonly endometriosis or adenomyosis, and less commonly fibroids or pelvic inflammatory disease, typically developing later in reproductive life than primary dysmenorrhoea, with the specific underlying cause requiring targeted investigation and treatment addressing the pathology itself rather than symptomatic pain relief alone.

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Fill in the blank: Primary dysmenorrhoea reflects excessive endometrial _____ production driving painful uterine contraction. Secondary dysmenorrhoea most commonly results from endometriosis or _____.

Category	Key Points
Menorrhagia causes (PALM)	- **Polyp**: endometrial or cervical - **Adenomyosis**: endometrial tissue within myometrium - **Leiomyoma**: fibroids, especially submucosal - **Malignancy/Hyperplasia**: endometrial carcinoma or atypical hyperplasia
Menorrhagia causes (COEIN)	- **Coagulopathy**: bleeding disorders (e.g., von Willebrand disease) - **Ovulatory dysfunction**: anovulation, PCOS - **Endometrial**: local endometrial hemostatic dysfunction - **Iatrogenic**: medications (anticoagulants, IUDs) - **Not yet classified**: rare or undefined causes
Primary dysmenorrhoea	- Occurs in adolescents/young women - No pelvic pathology - Due to prostaglandin-mediated uterine contractions - Presents as cramping pain during menstruation
Secondary dysmenorrhoea	- Occurs later in reproductive life - Associated with pelvic pathology (endometriosis, adenomyosis, fibroids, PID) - Pain may start before menstruation and persist - Often progressive and resistant to simple analgesia

Table 1.2: Menorrhagia causes and comparison of primary and secondary dysmenorrhoea.

Pilot questions 1.2

1. Define menorrhagia. (Linked to SLO 1.3)
2. Describe the causes of menorrhagia using the PALM-COEIN classification. (Linked to SLO 1.3)
3. Describe the evaluation of a woman presenting with menorrhagia. (Linked to SLO 1.4)
4. Describe the medical and surgical management options for menorrhagia. (Linked to SLO 1.4)
5. Distinguish primary from secondary dysmenorrhoea. (Linked to SLO 1.4)

1.3 Galactorrhoea and Hirsutism

1.3.1 Galactorrhoea: causes and evaluation

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Galactorrhoea describes inappropriate lactation occurring outside the context of pregnancy and breastfeeding, most commonly resulting from hyperprolactinaemia, whether from a prolactin-secreting pituitary adenoma, certain medications (including some antipsychotics and antiemetics), hypothyroidism, or, less commonly, chest wall stimulation or trauma, with each requiring specific consideration in the differential diagnostic workup.

Evaluation of galactorrhoea includes serum prolactin measurement, thyroid function tests to exclude hypothyroidism as an underlying cause, a detailed medication history, and, where prolactin is significantly elevated without another identified cause, pituitary imaging by MRI to identify or exclude a prolactin-secreting adenoma, with the specific treatment approach directly guided by the underlying cause identified.

Fill in the blank: Galactorrhoea most commonly results from _____, whether from a pituitary adenoma, medication, or hypothyroidism. Where prolactin is significantly elevated without another cause, pituitary imaging by _____ is used to identify a prolactin-secreting adenoma.

1.3.2 Hirsutism: definition and causes

Hirsutism describes excessive terminal hair growth in a male-pattern distribution in a woman, reflecting increased androgen production or, less commonly, increased peripheral tissue sensitivity to normal circulating androgen levels, distinguished from hypertrichosis (generalised excessive hair growth not specifically following a male pattern and not androgen-dependent).

Causes of hirsutism include polycystic ovarian syndrome (by far the most common cause), other causes of androgen excess including congenital adrenal hyperplasia and, rarely, an androgen-secreting ovarian or adrenal tumour, and certain medications, with the specific pattern, severity, and rate of onset of hirsutism, alongside any associated features such as virilisation, genuinely important in guiding the differential diagnosis and required investigation.

Fill in the blank: Hirsutism is distinguished from hypertrichosis, which is generalised excessive hair growth not specifically androgen-_____. Polycystic ovarian syndrome is by far the most common cause of _____.

1.3.3 Polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) is diagnosed using the Rotterdam criteria, requiring at least two of three features: oligo-ovulation or anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovarian morphology on ultrasound, with other causes of these specific features actively excluded before a confident diagnosis of PCOS is made.

PCOS is associated with a range of long-term metabolic implications beyond its immediate reproductive features, including insulin resistance, an increased risk of type 2 diabetes mellitus, dyslipidaemia, and endometrial hyperplasia from chronic anovulation and unopposed oestrogen exposure, meaning comprehensive management genuinely extends beyond addressing the presenting reproductive symptom alone to encompass this broader metabolic risk profile.

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Fill in the blank: PCOS is diagnosed using the Rotterdam criteria, requiring at least two of three features, including polycystic ovarian morphology on _____. PCOS is associated with insulin resistance and an increased risk of type 2 _____ mellitus.

Component	Key Points
PCOS: Rotterdam Criteria	Diagnosis requires **2 of 3**: - Oligo/anovulation - Clinical or biochemical hyperandrogenism - Polycystic ovaries on ultrasound
Galactorrhoea: Causes	- Hyperprolactinaemia - Pituitary adenoma - Hypothyroidism - Medications (antipsychotics, antidepressants) - Chest wall stimulation
Hirsutism: Causes	- PCOS - Congenital adrenal hyperplasia - Androgen-secreting tumors - Cushing's syndrome - Idiopathic hirsutism

Box 1.3: Diagnosis of PCOS and causes of galactorrhoea and hirsutism.

Pilot questions 1.3

1. Describe galactorrhoea and its causes. (Linked to SLO 1.5)
2. Describe the evaluation of galactorrhoea. (Linked to SLO 1.5)
3. Define hirsutism and distinguish it from hypertrichosis. (Linked to SLO 1.6)
4. List the causes of hirsutism. (Linked to SLO 1.6)
5. Describe the Rotterdam criteria for diagnosing PCOS and its long-term metabolic implications. (Linked to SLO 1.6)

1.4 Abnormal Uterine Bleeding Patterns

1.4.1 Intermenstrual bleeding

Intermenstrual bleeding describes bleeding occurring between otherwise recognisable, regular menstrual periods, with causes including hormonal contraceptive use (particularly during the early months of use, or with missed or delayed doses), cervical or endometrial polyps, cervical

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ectropion, and, less commonly, cervical or endometrial malignancy, meaning careful evaluation is genuinely warranted rather than automatic reassurance, particularly in an older woman.

Evaluation of intermenstrual bleeding includes a detailed history, examination including cervical visualisation and, where indicated, cervical cytology if not up to date, and transvaginal ultrasound to assess the endometrium and identify any structural cause, with the specific extent of investigation genuinely guided by the woman's age, risk factors, and the specific pattern and persistence of the bleeding itself.

Fill in the blank: Intermenstrual bleeding describes bleeding occurring between otherwise recognisable, regular menstrual _____. Evaluation of intermenstrual bleeding includes examination with cervical visualisation and, where indicated, cervical _____.

1.4.2 Postcoital bleeding

Postcoital bleeding describes bleeding occurring after sexual intercourse, most commonly resulting from cervical ectropion (a benign, physiological finding) or cervical or vaginal infection, though cervical malignancy must always be actively considered and excluded, particularly in a woman who has not attended regular cervical screening, given the genuinely serious consequence of a missed or delayed cancer diagnosis.

Evaluation of postcoital bleeding includes speculum examination to directly visualise the cervix, appropriate infection screening, and cervical cytology or, where clinically indicated, referral for colposcopy, with any visible cervical lesion warranting prompt biopsy regardless of the woman's cervical screening history or apparent age, given the genuine, though relatively uncommon, possibility of malignancy.

Fill in the blank: Postcoital bleeding most commonly results from cervical ectropion or cervical or vaginal _____. Any visible cervical lesion identified during evaluation of postcoital bleeding warrants prompt _____ regardless of screening history.

1.4.3 Postmenopausal bleeding

Postmenopausal bleeding describes vaginal bleeding occurring twelve months or more after the last menstrual period, requiring prompt investigation given the genuinely significant risk of underlying endometrial malignancy this specific symptom can represent, with endometrial cancer identified in a meaningful proportion of women presenting with this symptom, particularly with increasing age.

Evaluation of postmenopausal bleeding begins with transvaginal ultrasound measurement of endometrial thickness, with a thin endometrium considerably reassuring against malignancy, while a thickened endometrium warrants endometrial sampling, either by outpatient pipelle biopsy or, where indicated, hysteroscopy with directed biopsy, providing definitive histological diagnosis and appropriately guiding subsequent management.

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Fill in the blank: Postmenopausal bleeding describes vaginal bleeding occurring _____ months or more after the last menstrual period. A thin endometrium on transvaginal ultrasound is considerably reassuring against endometrial _____.

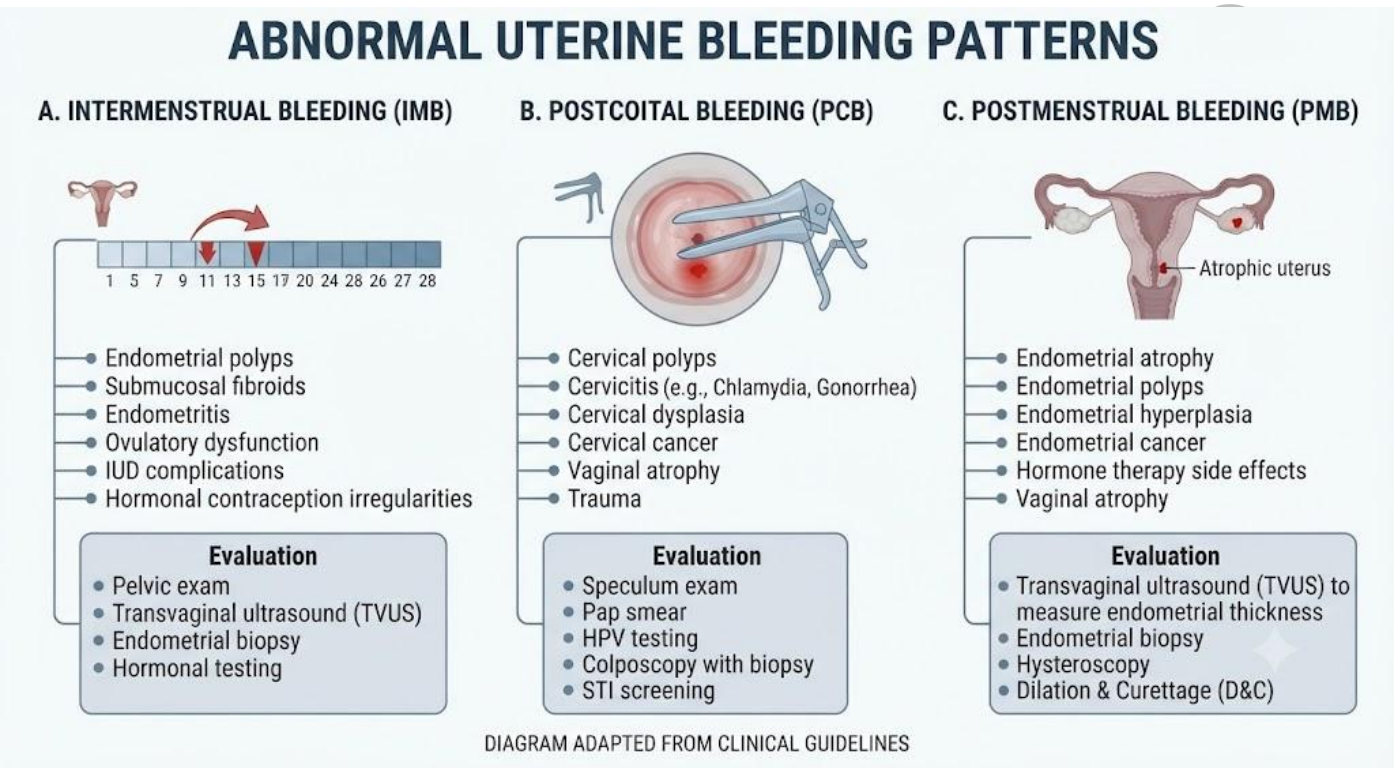

Figure 1.4: Comparison of intermenstrual, postcoital, and postmenopausal bleeding and their evaluation.

Pilot questions 1.4

1. Describe the causes of intermenstrual bleeding. (Linked to SLO 1.7)
2. Describe the evaluation of intermenstrual bleeding. (Linked to SLO 1.7)
3. Describe the causes and evaluation of postcoital bleeding. (Linked to SLO 1.7)
4. Define postmenopausal bleeding and explain why it requires prompt investigation. (Linked to SLO 1.8)
5. Describe the evaluation of postmenopausal bleeding. (Linked to SLO 1.8)

Series Summary

This Series has covered the normal menstrual cycle, its hormonal regulation and the parallel ovarian and endometrial cycles, followed by menorrhagia and dysmenorrhoea. It went on to

examine galactorrhoea, hirsutism, and polycystic ovarian syndrome, before concluding with intermenstrual, postcoital, and postmenopausal bleeding.

You should now be able to describe the hormonal regulation and phases of the menstrual cycle, define and manage menorrhagia and dysmenorrhoea, describe galactorrhoea, hirsutism, and PCOS, and describe the causes and evaluation of abnormal uterine bleeding patterns (Linked to SLOs 1.1 to 1.8).

Glossary of Terms

- **Corpus luteum:** the structure formed from the ruptured ovarian follicle after ovulation, secreting progesterone during the luteal phase.
- **Dysmenorrhoea:** painful menstruation, classified as primary (without underlying pathology) or secondary (with an identifiable cause).
- **Galactorrhoea:** inappropriate lactation occurring outside the context of pregnancy and breastfeeding, most commonly from hyperprolactinaemia.
- **Hirsutism:** excessive terminal hair growth in a male-pattern distribution in a woman, reflecting androgen excess.
- **Menorrhagia (heavy menstrual bleeding):** excessive menstrual blood loss interfering with a woman's quality of life.
- **PALM-COEIN classification:** an internationally recognised system classifying the structural and non-structural causes of abnormal uterine bleeding.
- **Polycystic ovarian syndrome (PCOS):** a condition diagnosed by the Rotterdam criteria, involving oligo-ovulation, hyperandrogenism, and polycystic ovarian morphology.
- **Postmenopausal bleeding:** vaginal bleeding occurring twelve months or more after the last menstrual period, requiring prompt investigation.
- **Rotterdam criteria:** the diagnostic criteria for PCOS, requiring at least two of three specified features.
- **Luteal phase:** the phase of the ovarian cycle following ovulation, during which the corpus luteum secretes progesterone.
- **Prostaglandins:** lipid compounds mediating uterine contraction, implicated in the pathophysiology of primary dysmenorrhoea.
- **Endometrial thickness:** a transvaginal ultrasound measurement used in the evaluation of postmenopausal bleeding.

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Concept Check Questions [Series 1]

Objective questions

1. The menstrual cycle is regulated by pulsatile secretion of gonadotropin-releasing hormone from the _____.
2. Ovulation is triggered by the LH surge, typically occurring around day _____ of a standard 28-day cycle.
3. Menorrhagia causes are formally classified using the internationally recognised _____ system.
4. PCOS is diagnosed using the Rotterdam criteria, requiring at least two of three features, including polycystic ovarian morphology on _____.
5. Postmenopausal bleeding describes vaginal bleeding occurring _____ months or more after the last menstrual period.

Short-answer questions

6. Explain the switch from negative to positive feedback triggering the LH surge. (Linked to SLO 1.1)
7. Distinguish primary from secondary dysmenorrhoea. (Linked to SLO 1.4)
8. Describe the evaluation of galactorrhoea. (Linked to SLO 1.5)
9. Describe the Rotterdam criteria for diagnosing PCOS and its long-term metabolic implications. (Linked to SLO 1.6)
10. Describe the causes and evaluation of postcoital bleeding. (Linked to SLO 1.7)

Long-answer questions

11. Describe the hormonal regulation of the menstrual cycle and the parallel ovarian and endometrial cycles. (Linked to SLO 1.1, SLO 1.2)
12. Define menorrhagia, describe its causes and evaluation, and describe its management alongside dysmenorrhoea. (Linked to SLO 1.3, SLO 1.4)
13. Describe galactorrhoea and its evaluation. (Linked to SLO 1.5)
14. Describe hirsutism and polycystic ovarian syndrome. (Linked to SLO 1.6)

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15. Describe the causes and evaluation of intermenstrual, postcoital, and postmenopausal bleeding. (Linked to SLO 1.7, SLO 1.8)

Answers to Concept Check Questions [Series 1]

Objective questions

1. Hypothalamus.
2. 14.
3. PALM-COEIN.
4. Ultrasound.
5. Twelve.

Short-answer questions

6. Sustained oestrogen from the dominant follicle switches from negative to positive feedback, triggering the LH surge and ovulation.
7. Primary dysmenorrhoea occurs without pelvic pathology from prostaglandin excess; secondary results from an identifiable cause such as endometriosis.
8. Serum prolactin, thyroid function tests, medication history, and pituitary MRI if prolactin is significantly elevated.
9. Two of three features: oligo-ovulation, hyperandrogenism, and polycystic morphology; associated with insulin resistance and diabetes risk.
10. Most commonly cervical ectropion or infection, though malignancy must be excluded by speculum examination and cytology or colposcopy.

Long-answer questions

11. **Basic response:** The menstrual cycle is regulated by the hypothalamic-pituitary-ovarian axis, with parallel ovarian and endometrial cycles driven by cyclical hormone changes.

Value-added response: The switch from negative to positive oestrogen feedback triggering the LH surge is a genuinely elegant physiological mechanism.

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12. **Basic response:** Menorrhagia is excessive bleeding affecting quality of life, classified by PALM-COEIN, managed medically with LNG-IUS first-line or surgically.

Value-added response: Primary dysmenorrhoea responds well to NSAIDs targeting prostaglandin synthesis, while secondary requires treating the underlying pathology.

13. **Basic response:** Galactorrhoea most commonly results from hyperprolactinaemia, evaluated by prolactin measurement, thyroid function, and pituitary imaging where indicated.

Value-added response: Treatment is directly guided by the underlying cause identified during evaluation.

14. **Basic response:** Hirsutism reflects androgen excess, most commonly from PCOS, diagnosed using the Rotterdam criteria requiring two of three specific features.

Value-added response: PCOS carries long-term metabolic implications including insulin resistance and increased type 2 diabetes risk.

15. **Basic response:** Intermenstrual, postcoital, and postmenopausal bleeding each warrant careful evaluation, with malignancy actively excluded in each case.

Value-added response: Postmenopausal bleeding carries particular significance given the genuine risk of underlying endometrial malignancy.

Answers to Pilot Questions [Series 1]

Part 1.1

1. GnRH from the hypothalamus stimulates FSH and LH release from the pituitary, acting on the ovary.
2. Sustained oestrogen from the dominant follicle switches from negative to positive feedback, triggering the LH surge.
3. Follicular phase, ovulation, and luteal phase.
4. The luteal phase is consistently around 14 days, while the follicular phase varies considerably between women and cycles.
5. Proliferative, secretory, and menstrual phases, with menstruation resulting from progesterone withdrawal and spiral artery vasoconstriction.

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Part 1.2

1. Excessive menstrual blood loss interfering with a woman's physical, social, emotional, or material quality of life.
2. PALM-COEIN classifies structural causes (polyp, adenomyosis, leiomyoma, malignancy) and non-structural causes (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, not classified).
3. Menstrual history, examination, transvaginal ultrasound, full blood count, and endometrial sampling in selected cases.
4. LNG-IUS first-line medically, alongside tranexamic acid and NSAIDs, with endometrial ablation or hysterectomy surgically.
5. Primary occurs without pathology from prostaglandin excess; secondary results from an identifiable cause such as endometriosis.

Part 1.3

1. Inappropriate lactation outside pregnancy and breastfeeding, most commonly from hyperprolactinaemia.
2. Serum prolactin, thyroid function tests, medication history, and pituitary MRI if indicated.
3. Excessive male-pattern terminal hair growth, distinguished from hypertrichosis which is not androgen-dependent.
4. PCOS (most common), congenital adrenal hyperplasia, androgen-secreting tumours, and certain medications.
5. Two of three features: oligo-ovulation, hyperandrogenism, and polycystic morphology; associated with insulin resistance and diabetes.

Part 1.4

1. Hormonal contraceptive use, cervical or endometrial polyps, cervical ectropion, and, less commonly, malignancy.
2. History, examination with cervical visualisation, cervical cytology, and transvaginal ultrasound.
3. Cervical ectropion or infection most commonly, with malignancy excluded by examination and cytology or colposcopy.

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4. Bleeding twelve months or more after the last period, requiring investigation given the genuine risk of endometrial malignancy.
5. Transvaginal ultrasound endometrial thickness measurement, followed by biopsy if thickened.

References and Attributions [Series 1]

Textual References

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- Munro, M. G., Critchley, H. O. D. and Fraser, I. S. (2018). The Two FIGO Systems for Normal and Abnormal Uterine Bleeding Symptoms and Classification of Causes of Abnormal Uterine Bleeding. International Journal of Gynecology and Obstetrics, 143(3), 393 to 408.
- Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004). Revised 2003 Consensus on Diagnostic Criteria and Long-Term Health Risks Related to Polycystic Ovary Syndrome. Fertility and Sterility, 81(1), 19 to 25.

Figures, Plates, Tables, and Boxes

- Figure 1.1: The menstrual cycle, showing parallel ovarian and endometrial phases with hormonal changes. AI-generated using the prompt: "Create a professional medical diagram titled The Menstrual Cycle, showing ovarian and endometrial phases aligned on a timeline with hormone curves. Clean clinical educational diagram style."
- Table 1.2: Menorrhagia causes and comparison of primary and secondary dysmenorrhoea. AI-generated using the prompt: "Create a clean reference table titled Menorrhagia and Dysmenorrhoea, listing PALM-COEIN causes and comparing primary versus secondary dysmenorrhoea. Simple clinical reference table style with outside border."
- Box 1.3: Diagnosis of PCOS and causes of galactorrhoea and hirsutism. AI-generated using the prompt: "Create a simple single-column reference box with an outside border titled PCOS, Galactorrhoea, and Hirsutism, listing Rotterdam criteria and causes. Clinical reference box style."
- Figure 1.4: Comparison of intermenstrual, postcoital, and postmenopausal bleeding and their evaluation. AI-generated using the prompt: "Create a professional medical diagram titled

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Abnormal Uterine Bleeding Patterns, comparing intermenstrual, postcoital, and postmenopausal bleeding causes and evaluation. Clean clinical educational diagram style."

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Course code: OBG 514

Course title: Reproductive Endocrinology and Fertility

Course credit load: 2 Units

Series 2: Amenorrhoea and Related Conditions

- **Part 2.1: Primary Amenorrhoea: Definition and Causes**
  - Sub Part 2.1.1: Definition and classification of amenorrhoea
  - Sub Part 2.1.2: Causes of primary amenorrhoea with normal secondary sexual characteristics
  - Sub Part 2.1.3: Causes of primary amenorrhoea with absent secondary sexual characteristics
- **Part 2.2: Primary Amenorrhoea: Investigation and Treatment**
  - Sub Part 2.2.1: Clinical evaluation of primary amenorrhoea
  - Sub Part 2.2.2: Investigations for primary amenorrhoea
  - Sub Part 2.2.3: Treatment of primary amenorrhoea
- **Part 2.3: Secondary Amenorrhoea: Definition and Aetiology**
  - Sub Part 2.3.1: Definition of secondary amenorrhoea
  - Sub Part 2.3.2: Hypothalamic and pituitary causes of secondary amenorrhoea
  - Sub Part 2.3.3: Ovarian and uterine causes of secondary amenorrhoea
- **Part 2.4: Secondary Amenorrhoea: Investigation and Treatment**
  - Sub Part 2.4.1: Clinical evaluation of secondary amenorrhoea
  - Sub Part 2.4.2: Investigations for secondary amenorrhoea
  - Sub Part 2.4.3: Treatment modalities for secondary amenorrhoea

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Introduction

In the last Series, we explored the menstrual cycle and its common disorders. We now turn to amenorrhoea itself, the complete absence of menstruation, a symptom with a genuinely broad differential diagnosis spanning anatomical abnormality present from birth to acquired hormonal disturbance developing later in life. Building on the hypothalamic-pituitary-ovarian axis established in Series 2, this Series equips you to systematically evaluate and manage both primary and secondary amenorrhoea.

The aim of this Series is to equip you with a thorough understanding of primary and secondary amenorrhoea, their definitions, causes, investigation, and treatment.

We shall commence this Series by examining the definition and causes of primary amenorrhoea. Next, we will consider its investigation and treatment. Following that, our attention turns to the definition and aetiology of secondary amenorrhoea. Finally, we will conclude by examining the investigation and treatment of secondary amenorrhoea.

Series Learning Outcomes

Upon completing this Series, you should be able to:

- **SLO 2.1:** define amenorrhoea and describe its classification,
- **SLO 2.2:** list the causes of primary amenorrhoea,
- **SLO 2.3:** describe the investigations for primary amenorrhoea,
- **SLO 2.4:** describe the treatment of primary amenorrhoea,
- **SLO 2.5:** define secondary amenorrhoea,
- **SLO 2.6:** enumerate the aetiology of secondary amenorrhoea,
- **SLO 2.7:** describe the investigations for secondary amenorrhoea, and
- **SLO 2.8:** describe the treatment modalities in secondary amenorrhoea.

2.1 Primary Amenorrhoea: Definition and Causes

2.1.1 Definition and classification of amenorrhoea

Amenorrhoea describes the absence of menstruation, classified as primary (failure of menarche to occur by age 15 in the presence of otherwise normal growth and secondary sexual

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characteristic development, or by age 13 in their absence) or secondary (absence of menstruation for six months or more, or three previous cycle intervals, in a woman who has previously menstruated normally), a fundamental distinction directly guiding the entire subsequent diagnostic approach.

This classification carries genuine practical importance because primary and secondary amenorrhoea reflect meaningfully different underlying differential diagnoses, with primary amenorrhoea more frequently reflecting a genetic, chromosomal, or anatomical abnormality present from birth, while secondary amenorrhoea more frequently reflects an acquired hormonal, structural, or functional disturbance developing later in reproductive life.

Fill in the blank: Primary amenorrhoea describes failure of menarche to occur by age _____ in the presence of otherwise normal development. Secondary amenorrhoea describes absence of menstruation for _____ months or more in a woman who has previously menstruated.

2.1.2 Causes of primary amenorrhoea with normal secondary sexual characteristics

Primary amenorrhoea occurring despite normal secondary sexual characteristic development (indicating adequate oestrogen exposure and, therefore, functioning ovaries) most commonly reflects an anatomical outflow tract abnormality, including imperforate hymen, transverse vaginal septum, or Mullerian agenesis (congenital absence of the uterus and upper vagina, also termed Mayer-Rokitansky-Kuster-Hauser syndrome), each preventing the visible passage of menstrual blood despite otherwise normal underlying hormonal function.

Imperforate hymen and transverse vaginal septum typically present with cyclical pelvic pain in the presence of amenorrhoea, reflecting accumulated menstrual blood (haematocolpos or haematometra) unable to escape, while Mullerian agenesis presents with painless primary amenorrhoea alone, given the genuine absence of a uterus in which menstrual blood could accumulate in the first place.

Fill in the blank: Mullerian agenesis, congenital absence of the uterus and upper vagina, is also termed _____ syndrome. Imperforate hymen and transverse vaginal septum typically present with cyclical pelvic pain from accumulated menstrual blood, termed haematocolpos or _____.

2.1.3 Causes of primary amenorrhoea with absent secondary sexual characteristics

Primary amenorrhoea occurring alongside absent or incomplete secondary sexual characteristic development (indicating inadequate oestrogen exposure) reflects either hypergonadotropic hypogonadism (ovarian failure, most commonly from Turner syndrome, a chromosomal abnormality in which one X chromosome is absent or structurally abnormal) or hypogonadotropic hypogonadism (inadequate pituitary gonadotropin stimulation of otherwise normal ovaries, from constitutional delay, significant chronic illness, excessive exercise or low body weight, or, less commonly, a specific hypothalamic or pituitary disorder).

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Distinguishing hypergonadotropic from hypogonadotropic hypogonadism relies principally on measurement of serum FSH and LH, elevated in hypergonadotropic hypogonadism (reflecting the pituitary's appropriate attempt to stimulate non-responsive, failing ovaries) and low or inappropriately normal in hypogonadotropic hypogonadism (reflecting inadequate central stimulation of otherwise potentially normal ovaries), a distinction of genuine diagnostic and prognostic importance.

Fill in the blank: Hypergonadotropic hypogonadism most commonly results from _____ syndrome, a chromosomal abnormality involving the X chromosome. FSH and LH are elevated in hypergonadotropic hypogonadism, reflecting the pituitary's attempt to stimulate non-responsive, failing _____.

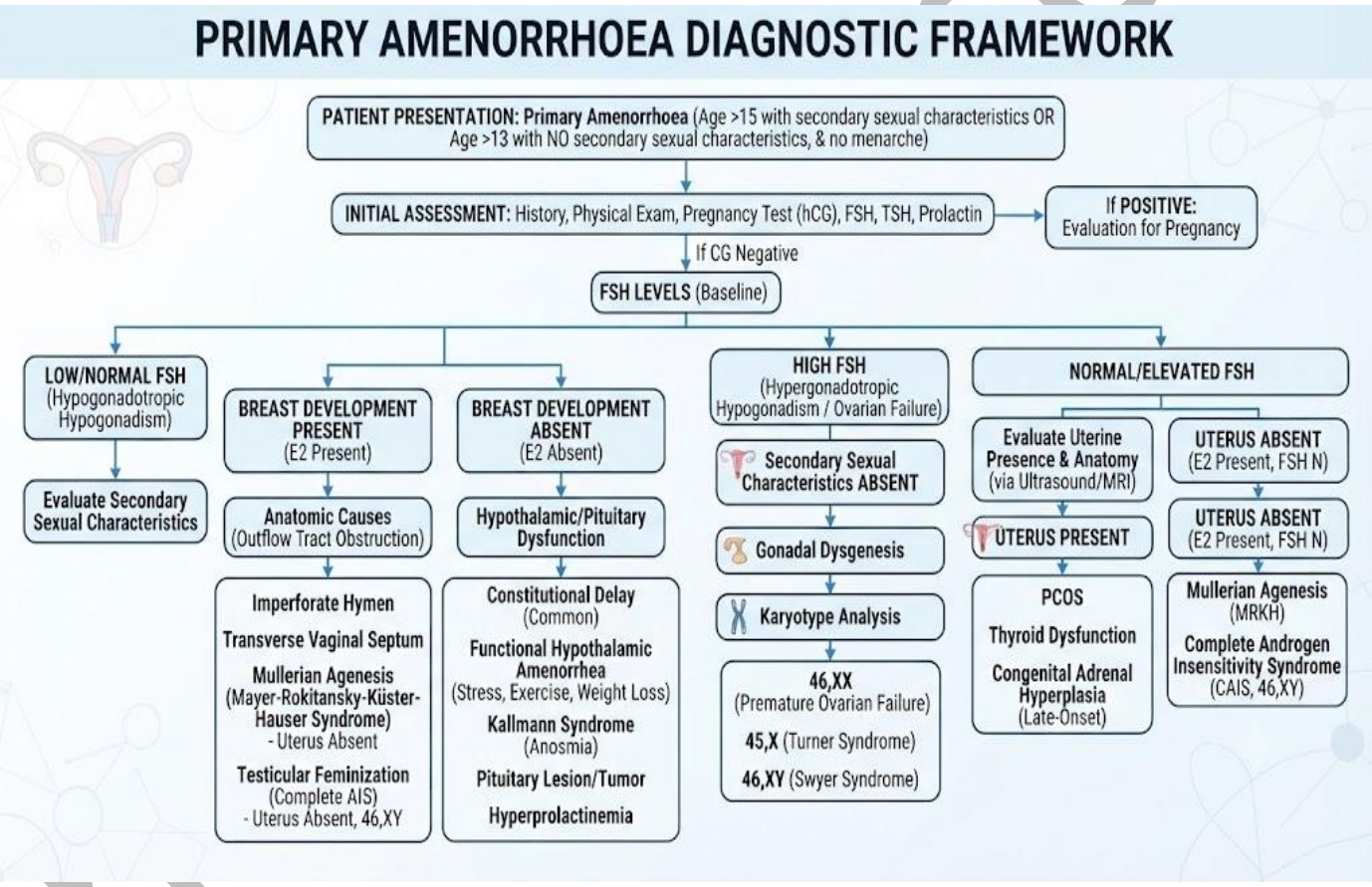

Figure 2.1: Diagnostic framework for primary amenorrhoea based on secondary sexual characteristics.

Pilot questions 2.1

- Define amenorrhoea and distinguish primary from secondary amenorrhoea. (Linked to SLO 2.1)
- Describe the causes of primary amenorrhoea with normal secondary sexual characteristics. (Linked to SLO 2.2)

- Distinguish imperforate hymen from Mullerian agenesis in their clinical presentation. (Linked to SLO 2.2)
- Describe the causes of primary amenorrhoea with absent secondary sexual characteristics. (Linked to SLO 2.2)
- Distinguish hypergonadotropic from hypogonadotropic hypogonadism using gonadotropin levels. (Linked to SLO 2.2)

2.2 Primary Amenorrhoea: Investigation and Treatment

2.2.1 Clinical evaluation of primary amenorrhoea

Clinical evaluation of primary amenorrhoea begins with a detailed history, including growth and pubertal development, any cyclical pain suggestive of an obstructive anatomical cause, family history, and chronic illness or lifestyle factors, alongside careful examination assessing secondary sexual characteristic development (using Tanner staging), height and body proportions, and, where appropriate, genital examination to identify any obvious structural abnormality.

Examination findings including short stature and specific dysmorphic features may suggest Turner syndrome, while a palpable pelvic mass with cyclical pain may suggest an obstructive outflow tract abnormality such as imperforate hymen, meaning careful, structured clinical assessment frequently provides genuinely valuable diagnostic clues even before any specific laboratory or imaging investigation is undertaken.

Fill in the blank: Clinical evaluation of primary amenorrhoea assesses secondary sexual characteristic development using _____ staging. Short stature and specific dysmorphic features on examination may suggest _____ syndrome.

2.2.2 Investigations for primary amenorrhoea

Initial investigations for primary amenorrhoea include serum FSH and LH (to distinguish hypergonadotropic from hypogonadotropic hypogonadism), pelvic ultrasound (to confirm the presence, absence, or structural abnormality of the uterus and identify any outflow tract obstruction), and karyotype analysis where Turner syndrome or another chromosomal abnormality is genuinely suspected on the basis of clinical or biochemical findings.

Further, more targeted investigation is guided by these initial findings, including specific hormonal testing (thyroid function, prolactin) where a hypothalamic or pituitary cause is suspected, and, where a structural genital tract abnormality is identified or strongly suspected,

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MRI to provide more detailed anatomical characterisation before any surgical intervention is planned.

Fill in the blank: Serum FSH and LH testing distinguishes hypergonadotropic from hypogonadotropic _____ in primary amenorrhoea. Karyotype analysis is performed where Turner syndrome or another chromosomal abnormality is genuinely _____.

2.2.3 Treatment of primary amenorrhoea

Treatment of primary amenorrhoea is genuinely directed at the specific underlying cause: surgical correction for an obstructive anatomical abnormality such as imperforate hymen, hormone replacement therapy to induce and maintain secondary sexual characteristic development and protect long-term bone health in hypergonadotropic hypogonadism (including Turner syndrome), and treatment of the specific underlying cause, where genuinely identifiable, in hypogonadotropic hypogonadism.

Psychological support for the young woman and her family is a genuinely essential component of care throughout this diagnostic and treatment process, given the considerable emotional impact a diagnosis affecting pubertal development, and, in some cases, future fertility, can understandably have, with clear, honest, age-appropriate communication and, where relevant, fertility counselling forming an integral part of comprehensive management.

Fill in the blank: Treatment of primary amenorrhoea from an obstructive anatomical abnormality such as imperforate hymen is generally _____. Hormone replacement therapy is used in hypergonadotropic hypogonadism to induce secondary sexual characteristics and protect long-term _____ health.

Investigation	Purpose	Treatment (by cause)
History & exam	Assess pubertal development, secondary sexual characteristics, genital anomalies	Tailored to underlying cause
Pregnancy test	Exclude pregnancy	If positive → manage as pregnancy
Hormonal profile **(FSH, LH, prolactin, TSH, estradiol)**	Differentiate ovarian, pituitary, hypothalamic causes	- Hypogonadotropic hypogonadism → lifestyle, pulsatile GnRH - Hyperprolactinaemia → dopamine agonists - Thyroid disease → thyroid replacement
Pelvic ultrasound	Assess uterus, ovaries, structural anomalies	- Müllerian agenesis → surgical correction/counseling - Gonadal dysgenesis (Turner) → hormone replacement
Karyotype analysis	Detect chromosomal abnormalities (Turner, AIS, Swyer syndrome)	- Turner syndrome → estrogen/progestin therapy - AIS → gonadectomy after puberty, hormone therapy

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Investigation	Purpose	Treatment (by cause)
MRI brain/pituitary	Evaluate pituitary or hypothalamic lesions	- Pituitary adenoma → medical/surgical management

Table 2.2: Investigations and treatment of primary amenorrhoea.

Pilot questions 2.2

1. Describe the clinical evaluation of a young woman with primary amenorrhoea. (Linked to SLO 2.3)
2. Describe the initial investigations for primary amenorrhoea. (Linked to SLO 2.3)
3. Describe the indications for karyotype analysis and pelvic MRI in primary amenorrhoea. (Linked to SLO 2.3)
4. Describe the treatment of primary amenorrhoea according to underlying cause. (Linked to SLO 2.4)
5. Explain the importance of psychological support in managing primary amenorrhoea. (Linked to SLO 2.4)

2.3 Secondary Amenorrhoea: Definition and Aetiology

2.3.1 Definition of secondary amenorrhoea

Secondary amenorrhoea is defined as the absence of menstruation for six months or more, or for three previous cycle intervals, in a woman who has previously menstruated normally, with pregnancy always the first, genuinely essential diagnosis to exclude in any woman of reproductive age presenting with this symptom, regardless of how unlikely pregnancy might initially seem based on the history alone.

Once pregnancy has been confidently excluded secondary amenorrhoea reflects disruption at any level of the hypothalamic-pituitary-ovarian axis discussed in Series 2, or, less commonly, a structural uterine abnormality preventing menstrual flow despite otherwise normal underlying hormonal function, meaning a structured, systematic approach considering each level of this axis genuinely helps organise the subsequent differential diagnosis and investigation.

Fill in the blank: Secondary amenorrhoea is defined as the absence of menstruation for six months or more in a woman who has previously _____. Pregnancy is always the first, genuinely essential diagnosis to _____ in any woman of reproductive age with this symptom.

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2.3.2 Hypothalamic and pituitary causes of secondary amenorrhoea

Hypothalamic causes of secondary amenorrhoea include functional hypothalamic amenorrhoea (resulting from significant stress, excessive exercise, or low body weight, including that from an eating disorder, each disrupting normal pulsatile GnRH secretion), and, less commonly, an underlying structural hypothalamic lesion, with functional hypothalamic amenorrhoea representing a genuinely common, important cause in young, active women.

Pituitary causes of secondary amenorrhoea include hyperprolactinaemia (from a prolactin-secreting adenoma or other cause, discussed in Series 2 of this course, disrupting normal GnRH pulsatility through its direct inhibitory effect), and, less commonly, other pituitary pathology or Sheehan's syndrome (pituitary infarction following severe postpartum haemorrhage, discussed elsewhere in this broader curriculum).

Fill in the blank: Functional hypothalamic amenorrhoea results from significant stress, excessive exercise, or low body weight, each disrupting normal pulsatile _____ secretion. Hyperprolactinaemia disrupts normal GnRH pulsatility through its direct inhibitory _____.

2.3.3 Ovarian and uterine causes of secondary amenorrhoea

Ovarian causes of secondary amenorrhoea include polycystic ovarian syndrome (a genuinely common cause given the chronic anovulation this condition causes), premature ovarian insufficiency (loss of normal ovarian function before age 40, whether idiopathic, genetic, autoimmune, or following chemotherapy or radiotherapy), and menopause itself, where secondary amenorrhoea occurs at the genuinely expected, physiological time of life.

Uterine causes of secondary amenorrhoea are considerably less common, principally intrauterine adhesions (Asherman syndrome, typically resulting from previous uterine surgery, most commonly following pregnancy-related curettage), a specific cause of genuine practical importance to actively exclude in a woman with a relevant surgical history and otherwise unexplained secondary amenorrhoea.

Fill in the blank: Premature ovarian insufficiency describes loss of normal ovarian function before age _____. Intrauterine adhesions, termed _____ syndrome, are a uterine cause of secondary amenorrhoea typically resulting from previous uterine surgery.

Level	Key Causes
Hypothalamic	- Stress, weight loss, excessive exercise - Chronic illness - Functional hypothalamic amenorrhoea
Pituitary	- Hyperprolactinaemia - Pituitary adenoma - Sheehan’s syndrome
Ovarian	- Polycystic ovary syndrome (PCOS) - Premature ovarian insufficiency - Resistant ovary syndrome

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Level	Key Causes
Uterine	- Asherman's syndrome (intrauterine adhesions) - Endometrial destruction (infection, curettage) - Congenital absence of endometrium

Box 2.3: Causes of secondary amenorrhoea organised by anatomical level.

Pilot questions 2.3

1. Define secondary amenorrhoea and explain why pregnancy must always be excluded first. (Linked to SLO 2.5)
2. Describe the hypothalamic causes of secondary amenorrhoea. (Linked to SLO 2.6)
3. Describe the pituitary causes of secondary amenorrhoea. (Linked to SLO 2.6)
4. Describe the ovarian causes of secondary amenorrhoea. (Linked to SLO 2.6)
5. Describe Asherman syndrome as a uterine cause of secondary amenorrhoea. (Linked to SLO 2.6)

2.4 Secondary Amenorrhoea: Investigation and Treatment

2.4.1 Clinical evaluation of secondary amenorrhoea

Clinical evaluation of secondary amenorrhoea begins with a pregnancy test in every case, followed by a detailed history covering the specific pattern and duration of amenorrhoea, associated symptoms (galactorrhoea, hirsutism, hot flushes, or symptoms suggestive of an eating disorder or excessive exercise), and relevant surgical history, alongside examination assessing body mass index, signs of hyperandrogenism, and any galactorrhoea.

This structured history and examination frequently provides valuable initial diagnostic clues genuinely narrowing the subsequent differential diagnosis before any laboratory investigation, with the specific combination of symptoms and signs present often pointing towards a particular level of the hypothalamic-pituitary-ovarian axis as the likely underlying cause.

Fill in the blank: Clinical evaluation of secondary amenorrhoea begins with a _____ test in every case. Examination assesses body mass index, signs of hyperandrogenism, and any _____.

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2.4.2 Investigations for secondary amenorrhoea

Initial investigations for secondary amenorrhoea include serum FSH and LH, prolactin, thyroid function tests, and, where hyperandrogenism is present, testosterone, with an elevated FSH suggesting ovarian failure or premature ovarian insufficiency, and a low or normal FSH with low oestrogen suggesting a hypothalamic or pituitary cause requiring further, targeted evaluation.

Further, more targeted investigation is guided by these initial findings, including pelvic ultrasound where PCOS or a structural cause is suspected, pituitary MRI where prolactin is significantly elevated or another pituitary cause is suspected, and, where Asherman syndrome is genuinely suspected on the basis of relevant surgical history, hysteroscopy for direct visualisation of the uterine cavity.

Fill in the blank: An elevated FSH in secondary amenorrhoea suggests ovarian failure or premature ovarian _____. Where Asherman syndrome is suspected, _____ allows direct visualisation of the uterine cavity.

2.4.3 Treatment modalities for secondary amenorrhoea

Treatment of secondary amenorrhoea is genuinely directed at the specific underlying cause: lifestyle modification and psychological support for functional hypothalamic amenorrhoea, dopamine agonist therapy for hyperprolactinaemia, weight management and metabolic treatment for PCOS, hormone replacement therapy for premature ovarian insufficiency, and hysteroscopic adhesiolysis for confirmed Asherman syndrome.

Where fertility is genuinely desired specific treatment is directed towards restoring ovulation, whether through addressing the underlying cause directly, ovulation induction medication, or, in some cases, assisted reproductive techniques discussed later in this course, with the specific approach genuinely individualised according to the underlying cause, the woman's own reproductive goals, and her broader clinical circumstances.

Fill in the blank: Treatment of hyperprolactinaemia-related secondary amenorrhoea uses dopamine _____ therapy. Confirmed Asherman syndrome is treated with hysteroscopic _____.

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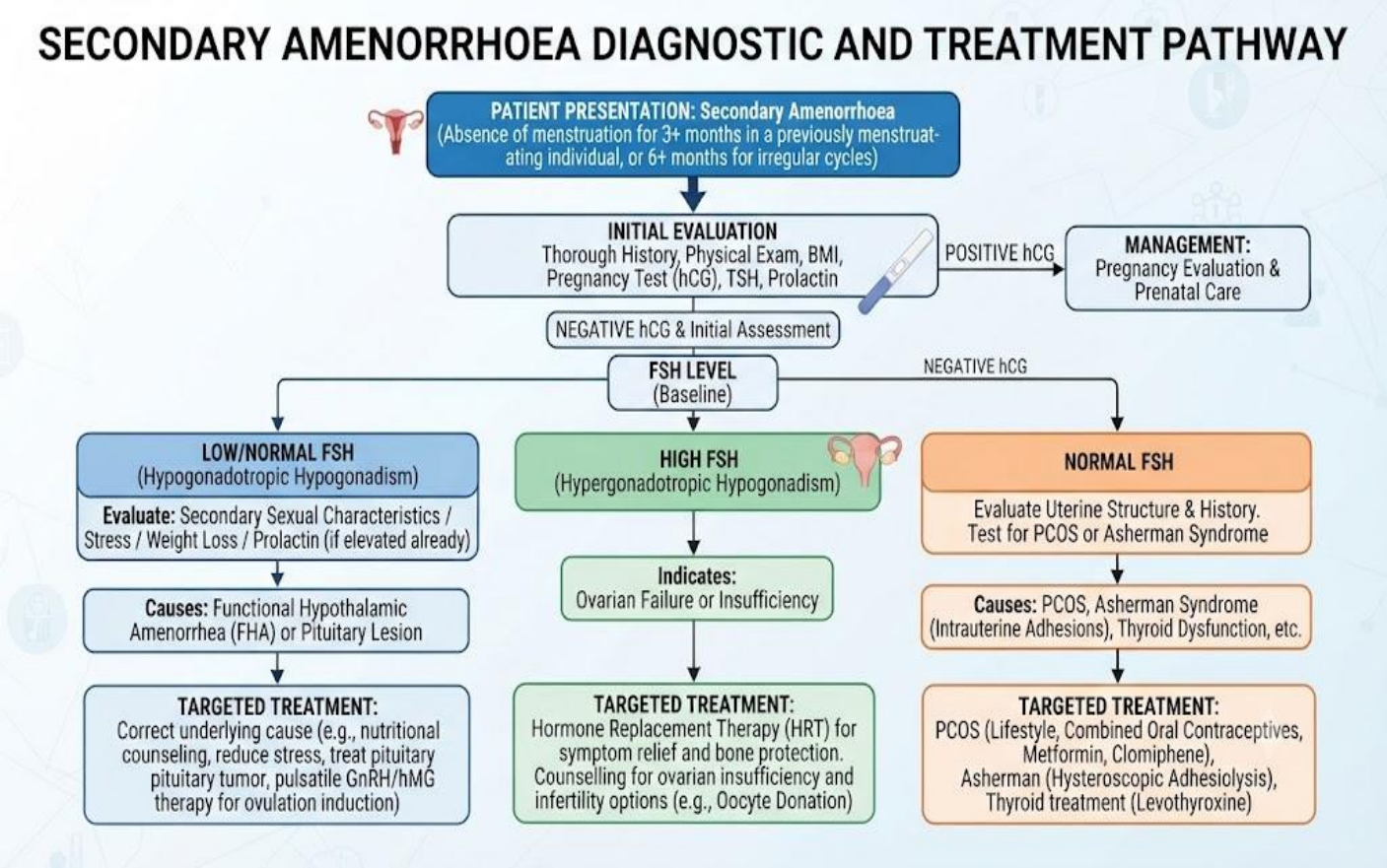

Figure 2.4: Diagnostic and treatment pathway for secondary amenorrhoea.

Pilot questions 2.4

1. Describe the clinical evaluation of a woman with secondary amenorrhoea. (Linked to SLO 2.7)
2. Describe the initial investigations for secondary amenorrhoea and their interpretation. (Linked to SLO 2.7)
3. Describe the further targeted investigations used in secondary amenorrhoea. (Linked to SLO 2.7)
4. Describe the treatment modalities for secondary amenorrhoea by underlying cause. (Linked to SLO 2.8)
5. Describe the treatment approach when fertility is genuinely desired in secondary amenorrhoea. (Linked to SLO 2.8)

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Series Summary

This Series has covered the definition and causes of primary amenorrhoea, followed by its investigation and treatment. It went on to examine the definition and aetiology of secondary amenorrhoea, before concluding with its investigation and treatment.

You should now be able to define amenorrhoea, list and investigate the causes of primary amenorrhoea and describe its treatment, define secondary amenorrhoea, enumerate its aetiology, and describe its investigation and treatment modalities (Linked to SLOs 2.1 to 2.8).

Glossary of Terms

1. **Asherman syndrome:** intrauterine adhesions, typically resulting from previous uterine surgery, a uterine cause of secondary amenorrhoea.
2. **Functional hypothalamic amenorrhoea:** amenorrhoea resulting from stress, excessive exercise, or low body weight disrupting pulsatile GnRH secretion.
3. **Hypergonadotropic hypogonadism:** ovarian failure with elevated gonadotropins, most commonly from Turner syndrome.
4. **Hypogonadotropic hypogonadism:** inadequate pituitary gonadotropin stimulation of otherwise normal ovaries.
5. **Imperforate hymen:** a congenital anomaly preventing menstrual outflow, presenting with cyclical pain and primary amenorrhoea.
6. **Mullerian agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome):** congenital absence of the uterus and upper vagina, presenting with painless primary amenorrhoea.
7. **Premature ovarian insufficiency:** loss of normal ovarian function before age 40.
8. **Primary amenorrhoea:** failure of menarche to occur by age 15 with normal development, or by age 13 without it.
9. **Secondary amenorrhoea:** absence of menstruation for six months or more in a woman who has previously menstruated.
10. **Tanner staging:** a system for assessing the stage of pubertal secondary sexual characteristic development.
11. **Turner syndrome:** a chromosomal abnormality involving an absent or structurally abnormal X chromosome, causing hypergonadotropic hypogonadism.

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12. **Haematocolpos:** accumulation of menstrual blood within the vagina, resulting from an obstructive outflow tract abnormality.

Concept Check Questions [Series 2]

Objective questions

- Primary amenorrhoea describes failure of menarche to occur by age _____ in the presence of otherwise normal development.
- Mullerian agenesis is also termed _____ syndrome.
- Hypergonadotropic hypogonadism most commonly results from _____ syndrome.
- Premature ovarian insufficiency describes loss of normal ovarian function before age _____.
- An elevated FSH in secondary amenorrhoea suggests ovarian failure or premature ovarian _____.

Short-answer questions

1. Distinguish hypergonadotropic from hypogonadotropic hypogonadism using gonadotropin levels. (Linked to SLO 2.2)
2. Describe the indications for karyotype analysis and pelvic MRI in primary amenorrhoea. (Linked to SLO 2.3)
3. Describe the hypothalamic causes of secondary amenorrhoea. (Linked to SLO 2.6)
4. Describe Asherman syndrome as a uterine cause of secondary amenorrhoea. (Linked to SLO 2.6)
5. Describe the treatment approach when fertility is genuinely desired in secondary amenorrhoea. (Linked to SLO 2.8)

Long-answer questions

6. Define amenorrhoea and describe the causes of primary amenorrhoea. (Linked to SLO 2.1, SLO 2.2)

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7. Describe the investigations and treatment of primary amenorrhoea. (Linked to SLO 2.3, SLO 2.4)
8. Define secondary amenorrhoea and enumerate its aetiology. (Linked to SLO 2.5, SLO 2.6)
9. Describe the investigations for secondary amenorrhoea. (Linked to SLO 2.7)
10. Describe the treatment modalities in secondary amenorrhoea. (Linked to SLO 2.8)

Answers to Concept Check Questions [Series 2]

Objective questions

11. 15.
12. Mayer-Rokitansky-Kuster-Hauser.
13. Turner.
14. 40.
15. Insufficiency.

Short-answer questions

16. FSH and LH are elevated in hypergonadotropic hypogonadism and low or inappropriately normal in hypogonadotropic hypogonadism.
17. Karyotype where Turner syndrome or chromosomal abnormality is suspected; MRI where a structural genital tract abnormality is identified.
18. Functional hypothalamic amenorrhoea from stress, excessive exercise, or low body weight, and, less commonly, structural lesions.
19. Intrauterine adhesions typically from previous uterine surgery, most commonly pregnancy-related curettage.
20. Treatment targets restoring ovulation through addressing the cause, ovulation induction, or assisted reproductive techniques.

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Long-answer questions

21. **Basic response:** Amenorrhoea is classified as primary or secondary, with primary amenorrhoea reflecting anatomical or genetic causes, further divided by presence or absence of secondary sexual characteristics.

Value-added response: This classification directly guides the diagnostic approach, given the genuinely different underlying causes each category typically represents.

22. **Basic response:** Investigation combines history, examination, FSH/LH, pelvic ultrasound, and karyotype where indicated, with treatment directed at the specific cause identified.

Value-added response: Psychological support is genuinely essential given the emotional impact on pubertal development and future fertility.

23. **Basic response:** Secondary amenorrhoea is absence of menstruation for six months or more, with aetiology spanning hypothalamic, pituitary, ovarian, and uterine causes.

Value-added response: Pregnancy must always be excluded first, regardless of how unlikely it might seem based on the history alone.

24. **Basic response:** Investigation includes pregnancy test, FSH/LH, prolactin, thyroid function, and targeted imaging or hysteroscopy guided by initial findings.

Value-added response: The combination of symptoms and signs often points towards a particular level of the axis before laboratory testing.

25. **Basic response:** Treatment is directed at the underlying cause, from lifestyle modification to dopamine agonists, hormone replacement, or hysteroscopic adhesiolysis.

Value-added response: Where fertility is desired, treatment is specifically directed towards restoring ovulation according to individual circumstances.

Answers to Pilot Questions [Series 2]

Part 2.1

1. Absence of menstruation, classified as primary (failure of menarche) or secondary (absence after previous normal menstruation).

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2. Anatomical outflow tract abnormalities including imperforate hymen, transverse vaginal septum, or Mullerian agenesis.
3. Imperforate hymen presents with cyclical pain from accumulated blood; Mullerian agenesis presents with painless amenorrhoea given the absent uterus.
4. Hypergonadotropic hypogonadism (ovarian failure, e.g. Turner syndrome) or hypogonadotropic hypogonadism (inadequate pituitary stimulation).
5. FSH and LH are elevated in hypergonadotropic hypogonadism, low or inappropriately normal in hypogonadotropic hypogonadism.

Part 2.2

6. History of growth and pubertal development, cyclical pain, family history; examination of Tanner staging, height, and genital anatomy.
7. FSH and LH, pelvic ultrasound, and karyotype analysis where chromosomal abnormality is suspected.
8. Karyotype where Turner syndrome is suspected; MRI where a structural genital tract abnormality is identified.
9. Surgical correction for anatomical obstruction, hormone replacement for hypergonadotropic hypogonadism, and cause-specific treatment for hypogonadotropic hypogonadism.
10. Considerable emotional impact from a diagnosis affecting pubertal development and future fertility warrants clear, compassionate support.

Part 2.3

11. Absence of menstruation for six months or more in a woman who has previously menstruated; pregnancy must always be excluded first.
12. Functional hypothalamic amenorrhoea from stress, exercise, or low body weight, and less commonly structural lesions.
13. Hyperprolactinaemia, other pituitary pathology, and Sheehan's syndrome.
14. PCOS, premature ovarian insufficiency, and menopause.

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15. Intrauterine adhesions typically from previous uterine surgery, most commonly pregnancy-related curettage.

Part 2.4

1. Pregnancy test, history of associated symptoms, and examination of BMI, hyperandrogenism, and galactorrhoea.
2. FSH/LH, prolactin, and thyroid function; elevated FSH suggests ovarian failure, low FSH with low oestrogen suggests hypothalamic or pituitary cause.
3. Pelvic ultrasound, pituitary MRI, and hysteroscopy guided by initial findings.
4. Lifestyle modification, dopamine agonists, weight management, hormone replacement, or hysteroscopic adhesiolysis according to cause.
5. Treatment targets restoring ovulation through addressing the cause, ovulation induction, or assisted reproductive techniques.

References and Attributions [Series 2]

Textual References

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2. American College of Obstetricians and Gynecologists (2018). Primary Ovarian Insufficiency in Adolescents and Young Women. Committee Opinion No. 605.
3. European Society for Human Reproduction and Embryology (2016). Management of Women with Premature Ovarian Insufficiency: Guideline of the ESHRE. ESHRE Guideline Group.
4. Berek, J. S. and Berek, D. L. (2019). Berek and Novak's Gynecology (16th ed.). Wolters Kluwer.

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Figures, Plates, Tables, and Boxes

1. Figure 2.1: Diagnostic framework for primary amenorrhoea based on secondary sexual characteristics. AI-generated using the prompt: "Create a professional medical flowchart titled Primary Amenorrhoea Diagnostic Framework, branching by secondary sexual characteristics and gonadotropin status. Clean clinical educational diagram style."
2. Table 2.2: Investigations and treatment of primary amenorrhoea. AI-generated using the prompt: "Create a clean reference table titled Primary Amenorrhoea: Investigation and Treatment, listing key investigations and treatment by cause. Simple clinical reference table style with outside border."
3. Box 2.3: Causes of secondary amenorrhoea organised by anatomical level. AI-generated using the prompt: "Create a simple single-column reference box with an outside border titled Causes of Secondary Amenorrhoea, organised by hypothalamic, pituitary, ovarian, and uterine level. Clinical reference box style."
4. Figure 2.4: Diagnostic and treatment pathway for secondary amenorrhoea. AI-generated using the prompt: "Create a professional medical flowchart titled Secondary Amenorrhoea Diagnostic and Treatment Pathway, showing pregnancy exclusion, FSH differentiation, and targeted treatment. Clean clinical educational diagram style."

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Course code: OBG 514

Course title: Reproductive Endocrinology and Fertility

Course credit load: 2 Units

Series 3: Climacteric and Menopause

- **Part 3.1: Physiology of the Climacteric and Menopause**
  - Sub Part 3.1.1: Definition of the climacteric and menopause
  - Sub Part 3.1.2: Hormonal changes at menopause
  - Sub Part 3.1.3: Stages of the menopausal transition
- **Part 3.2: Perimenopausal and Menopausal Symptoms**
  - Sub Part 3.2.1: Vasomotor symptoms
  - Sub Part 3.2.2: Urogenital and psychological symptoms
  - Sub Part 3.2.3: Long-term consequences of oestrogen deficiency
- **Part 3.3: Diagnosis and Investigation of Menopause**
  - Sub Part 3.3.1: Clinical diagnosis of menopause
  - Sub Part 3.3.2: Hormonal investigations
  - Sub Part 3.3.3: Differentiating menopause from other causes of symptoms
- **Part 3.4: Management of Menopause**
  - Sub Part 3.4.1: Hormone replacement therapy
  - Sub Part 3.4.2: Non-hormonal management and lifestyle measures
  - Sub Part 3.4.3: Premature ovarian insufficiency

Introduction

In the last Series, we explored amenorrhoea and its causes, investigation and treatment across the reproductive years. We now turn to the climacteric, the transitional phase during which ovarian function declines and eventually ceases, culminating in menopause. This transition affects every woman who lives beyond midlife, making it one of the most universally relevant topics in reproductive endocrinology.

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The climacteric brings characteristic hormonal changes, a wide range of physical and psychological symptoms, and important long-term health consequences related to sustained oestrogen deficiency, including bone loss and cardiovascular risk. Understanding the normal physiology of this transition provides the foundation for recognising when symptoms are menopausal in origin and when they warrant further investigation for an alternative cause.

This Series covers the physiology of the climacteric and menopause, the range of perimenopausal and menopausal symptoms and their long-term consequences, the clinical and hormonal approach to diagnosis, and the principles of management, including hormone replacement therapy and the distinct considerations that apply to premature ovarian insufficiency.

Series Learning Outcomes

At the end of this Series, students should be able to:

- **SLO 3.1:** define the climacteric and menopause,
- **SLO 3.2:** describe the hormonal changes that occur at menopause,
- **SLO 3.3:** enumerate the stages of the menopausal transition,
- **SLO 3.4:** describe the vasomotor, urogenital and psychological symptoms of the perimenopause,
- **SLO 3.5:** discuss the long-term health consequences of oestrogen deficiency after menopause,
- **SLO 3.6:** describe the clinical and hormonal diagnosis of menopause,
- **SLO 3.7:** discuss the indications, types and risks of hormone replacement therapy, and
- **SLO 3.8:** describe the presentation and management of premature ovarian insufficiency.

Part 3.1: Physiology of the Climacteric and Menopause

3.1.1 Definition of the climacteric and menopause

The climacteric is the transitional phase of a woman's life during which ovarian function progressively declines, beginning several years before the final menstrual period and extending into the years afterward. Menopause itself is defined retrospectively as the permanent cessation

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of menstruation, confirmed after twelve consecutive months of amenorrhoea with no other identifiable cause, and marks the point at which ovarian follicular activity has essentially ceased.

The average age at natural menopause is around 51 years, though the normal range extends from the mid-40s into the mid-50s. Menopause occurring before age 40 is termed premature ovarian insufficiency, while menopause between 40 and 45 years is termed early menopause. The perimenopause refers to the years of irregular cycles and fluctuating hormone levels immediately surrounding the final menstrual period.

Fill in the blank: Menopause is confirmed after _____ consecutive months of amenorrhoea. Menopause before age _____ is termed premature ovarian insufficiency.

3.1.2 Hormonal changes at menopause

The central hormonal event of menopause is the depletion of ovarian follicles, which reduces oestradiol production and removes the negative feedback that normally restrains pituitary gonadotropin secretion. As a result, follicle-stimulating hormone and luteinising hormone levels rise, often several-fold, while oestradiol levels fall progressively as the transition advances.

Inhibin B, produced by granulosa cells of developing follicles, also declines early in the transition and is one of the earliest hormonal markers of diminishing ovarian reserve, often falling before FSH begins to rise consistently. Progesterone production ceases once ovulation stops occurring, contributing to the irregular, often heavier bleeding that can characterise the late perimenopause before periods stop altogether.

Fill in the blank: Depletion of ovarian follicles removes negative feedback, causing _____ and LH to rise. _____ B declines early and is one of the earliest markers of diminishing ovarian reserve.

3.1.3 Stages of the menopausal transition

The menopausal transition is commonly described using staging systems such as STRAW, which divide the process into the late reproductive stage, the early and late menopausal transition, and early and late postmenopause, based primarily on menstrual cycle characteristics and hormone levels. The early transition is marked by subtle cycle length variability, while the late transition features longer intervals of amenorrhoea of 60 days or more.

Postmenopause begins at the final menstrual period and is divided into early postmenopause, encompassing the first several years when vasomotor symptoms are typically most prominent, and late postmenopause, when hormone levels have stabilised at a low level and long-term consequences such as bone loss become the dominant clinical concern.

Fill in the blank: The late menopausal transition features intervals of amenorrhoea of _____ days or more. Vasomotor symptoms are typically most prominent in _____ postmenopause.

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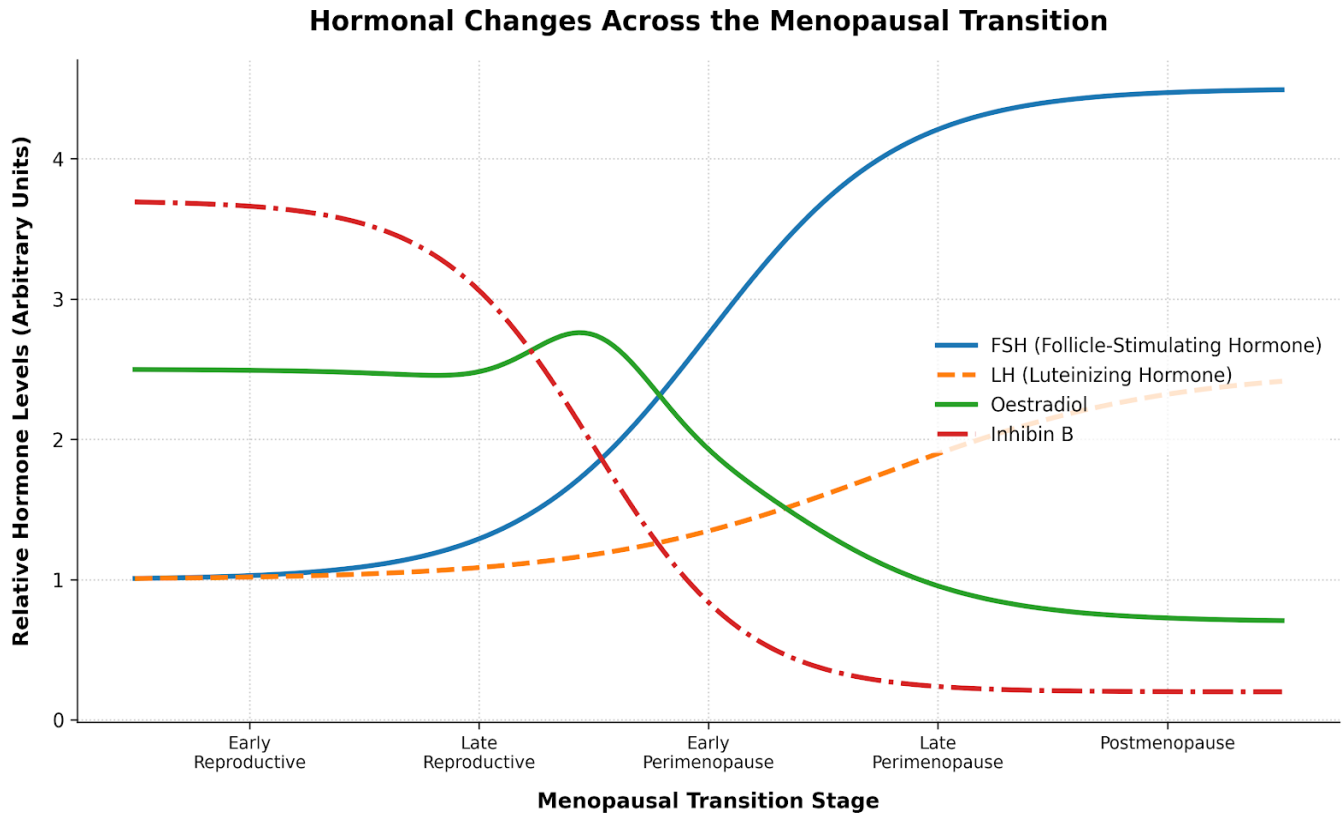

Figure 3.1: Hormonal changes across the menopausal transition.

Pilot questions 3.1

- Define the climacteric and distinguish it from menopause. (Linked to SLO 3.1)
- Describe the average age range at natural menopause and distinguish premature ovarian insufficiency from early menopause. (Linked to SLO 3.1)
- Describe the hormonal changes in FSH, LH and oestradiol that occur as ovarian follicles are depleted. (Linked to SLO 3.2)
- Describe the role of inhibin B as an early marker of diminishing ovarian reserve. (Linked to SLO 3.2)
- Enumerate the stages of the menopausal transition and describe the features that distinguish them. (Linked to SLO 3.3)

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Part 3.2: Perimenopausal and Menopausal Symptoms

3.2.1 Vasomotor symptoms

Vasomotor symptoms, principally hot flushes and night sweats, are the most characteristic feature of the menopausal transition, affecting most women to some degree and often beginning in the late perimenopause. A hot flush is a sudden sensation of heat, typically affecting the face, neck and chest, often accompanied by visible flushing, sweating and a subsequent chill, and usually lasting a few minutes.

Vasomotor symptoms result from oestrogen withdrawal narrowing the thermoregulatory zone in the hypothalamus, so that small changes in core body temperature trigger heat-dissipating responses such as sweating and peripheral vasodilation. Night sweats disrupt sleep and are a major contributor to the fatigue and reduced quality of life reported by many women during this period.

Fill in the blank: Vasomotor symptoms result from oestrogen withdrawal narrowing the _____ zone in the hypothalamus. Night sweats disrupt _____ and contribute to fatigue.

3.2.2 Urogenital and psychological symptoms

Declining oestrogen levels lead to thinning of the vaginal epithelium, reduced lubrication and loss of vaginal elasticity, collectively termed genitourinary syndrome of menopause, which can cause dyspareunia, vaginal dryness and irritation, alongside urinary symptoms such as urgency, frequency and recurrent urinary tract infection due to similar atrophic changes in the urethra and bladder trigone.

Psychological symptoms including mood lability, irritability, anxiety and difficulty concentrating are commonly reported during the perimenopause, though their relationship to hormonal change is complex and often compounded by sleep disruption from night sweats and by concurrent midlife psychosocial stressors, meaning a careful, holistic history is essential before attributing symptoms to menopause alone.

Fill in the blank: Genitourinary syndrome of menopause results from thinning of the _____ epithelium due to declining oestrogen. Psychological symptoms are often compounded by _____ disruption from night sweats.

3.2.3 Long-term consequences of oestrogen deficiency

Sustained oestrogen deficiency after menopause accelerates bone loss, as oestrogen normally restrains osteoclast activity, so its withdrawal leads to increased bone resorption relative to formation and a progressive fall in bone mineral density, substantially increasing the lifetime risk of osteoporosis and fragility fracture, particularly of the hip, spine and wrist.

Menopause is also associated with an increase in cardiovascular risk, as the favourable lipid profile and vascular protection conferred by oestrogen during the reproductive years diminishes, contributing, alongside age-related changes, to the narrowing of the gap in cardiovascular disease incidence between women and men that is typically observed after midlife.

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Fill in the blank: Oestrogen normally restrains _____ activity, so its withdrawal accelerates bone loss. Menopause is associated with increased _____ risk as vascular protection from oestrogen diminishes.

Body System	Common Symptoms
Vasomotor	Hot flashes, night sweats
Genitourinary	Vaginal dryness, dyspareunia, urinary frequency, recurrent urinary tract infections
Psychological	Mood swings, irritability, anxiety, depression, poor concentration
Neurological	Sleep disturbances, headaches, memory lapses
Musculoskeletal	Joint pain, muscle aches, decreased bone density (osteoporosis risk)
Dermatological	Dry skin, thinning hair, brittle nails
Cardiovascular	Palpitations, increased risk of hypertension and heart disease

Table 3.2: Perimenopausal and menopausal symptoms by system.

Pilot questions 3.2

1. Describe the clinical features and underlying mechanism of hot flushes. (Linked to SLO 3.4)
2. Explain why night sweats commonly disrupt sleep and contribute to fatigue. (Linked to SLO 3.4)
3. Describe the features of genitourinary syndrome of menopause. (Linked to SLO 3.4)
4. Discuss the psychological symptoms associated with the perimenopause and the caution needed in attributing them to menopause alone. (Linked to SLO 3.4)
5. Discuss the long-term consequences of oestrogen deficiency on bone and cardiovascular health. (Linked to SLO 3.5)

Part 3.3: Diagnosis and Investigation of Menopause

3.3.1 Clinical diagnosis of menopause

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In women over 45 years presenting with typical vasomotor symptoms and menstrual irregularity progressing to amenorrhoea, menopause is generally a clinical diagnosis based on the history alone, without the need for confirmatory hormonal testing, since natural fluctuation in hormone levels during the perimenopause makes a single measurement unreliable for diagnosis in this age group.

A careful history should establish the pattern of menstrual change, the nature and severity of vasomotor and other symptoms, relevant past medical and family history, including any personal or family history of breast cancer, venous thromboembolism or cardiovascular disease, all of which are relevant to subsequent decisions about hormone replacement therapy.

Fill in the blank: In women over _____ years with typical symptoms, menopause is generally diagnosed on _____ alone. A single hormone measurement is unreliable during the perimenopause due to natural fluctuation.

3.3.2 Hormonal investigations

Hormonal testing, principally serum FSH, is reserved for specific situations: women under 40 years with suspected premature ovarian insufficiency, women aged 40 to 45 years with menopausal symptoms where confirmation would guide management, and women in whom the diagnosis is otherwise unclear, such as those who have had a hysterectomy without oophorectomy and can no longer use menstrual pattern as a marker.

A persistently elevated FSH, generally above 25 to 30 international units per litre on two occasions several weeks apart, alongside a low oestradiol, supports a diagnosis of ovarian insufficiency, though a single normal result does not exclude the diagnosis given the fluctuating hormone levels characteristic of the perimenopausal transition.

Fill in the blank: Hormonal testing for menopause is reserved for women under _____ years with suspected premature ovarian insufficiency. A persistently elevated FSH with low _____ supports the diagnosis.

3.3.3 Differentiating menopause from other causes of symptoms

Several conditions can mimic menopausal symptoms and should be considered before attributing new symptoms to the climacteric, including thyroid dysfunction, which can cause menstrual irregularity, flushing and mood disturbance, and should be excluded with thyroid function testing where clinically indicated, particularly if symptoms are atypical.

Pregnancy must always be considered and excluded in a perimenopausal woman presenting with amenorrhoea, since ovulation can still occur intermittently during the perimenopause despite irregular cycles, and other causes of abnormal bleeding, including endometrial pathology, must be appropriately investigated in women with irregular or heavy bleeding rather than being assumed to be simply perimenopausal in origin.

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Fill in the blank: _____ dysfunction can mimic menopausal symptoms including flushing and mood disturbance. _____ must always be excluded in a perimenopausal woman presenting with amenorrhoea.

Clinical Situation
Premature Menopause Suspected
Uncertain Menstrual History
Atypical Symptom Presentation
Early Surgical Menopause
Differentiating Other Endocrine Disorders

Box 3.3: Indications for hormonal testing in suspected menopause.

Pilot questions 3.3

1. Describe the basis for clinical diagnosis of menopause in women over 45 years. (Linked to SLO 3.6)
2. Enumerate the specific situations in which hormonal testing for menopause is indicated. (Linked to SLO 3.6)
3. Describe the FSH and oestradiol findings that support a diagnosis of ovarian insufficiency. (Linked to SLO 3.6)
4. Discuss thyroid dysfunction as a differential diagnosis for menopausal symptoms. (Linked to SLO 3.6)
5. Explain why pregnancy must always be excluded in a perimenopausal woman with amenorrhoea. (Linked to SLO 3.6)

Part 3.4: Management of Menopause

3.4.1 Hormone replacement therapy

Hormone replacement therapy remains the most effective treatment for vasomotor symptoms and genitourinary syndrome of menopause, and is generally offered as combined oestrogen and progestogen therapy in women with an intact uterus, to protect against endometrial hyperplasia,

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or oestrogen alone in women who have had a hysterectomy, with the choice of route, including oral, transdermal or vaginal, guided by symptoms, risk factors and patient preference.

Hormone replacement therapy carries small increased risks of venous thromboembolism, particularly with oral formulations, and, with longer duration of combined use, a modest increase in breast cancer risk, meaning that the decision to prescribe and its duration should be individualised, balancing symptom severity and quality of life against personal risk factors, generally favouring the lowest effective dose for the shortest duration needed to control symptoms.

Fill in the blank: Women with an intact uterus require combined oestrogen and _____ therapy to protect the endometrium. HRT carries a small increased risk of venous _____, particularly with oral formulations.

3.4.2 Non-hormonal management and lifestyle measures

For women who cannot or prefer not to use hormone replacement therapy, non-hormonal options for vasomotor symptoms include certain antidepressants such as selective serotonin and serotonin-noradrenaline reuptake inhibitors, gabapentin, and clonidine, though these are generally less effective than hormone replacement therapy and are selected based on individual contraindications and symptom profile.

Lifestyle measures, including regular weight-bearing exercise, adequate calcium and vitamin D intake, smoking cessation, and avoidance of known symptom triggers such as caffeine, alcohol and spicy food, form an important adjunct to any pharmacological treatment and directly support the long-term goals of bone and cardiovascular health protection discussed earlier in this Series.

Fill in the blank: Non-hormonal options for vasomotor symptoms include SSRIs, gabapentin and _____. Regular weight-bearing exercise supports long-term _____ health.

3.4.3 Premature ovarian insufficiency

Premature ovarian insufficiency, defined as menopause before age 40, requires particular attention because affected women face a substantially longer duration of oestrogen deficiency than those with natural menopause, with correspondingly greater lifetime risk of osteoporosis and cardiovascular disease if hormone replacement is not provided, alongside the significant psychological impact of an unexpected loss of fertility.

Hormone replacement therapy is generally recommended for women with premature ovarian insufficiency at least until the average age of natural menopause, both to control symptoms and to provide the bone and cardiovascular protection that would otherwise have been provided by endogenous oestrogen, alongside appropriate fertility counselling and psychological support given the considerable emotional impact of the diagnosis.

Fill in the blank: Premature ovarian insufficiency is defined as menopause before age _____. HRT is generally recommended until at least the average age of natural _____.

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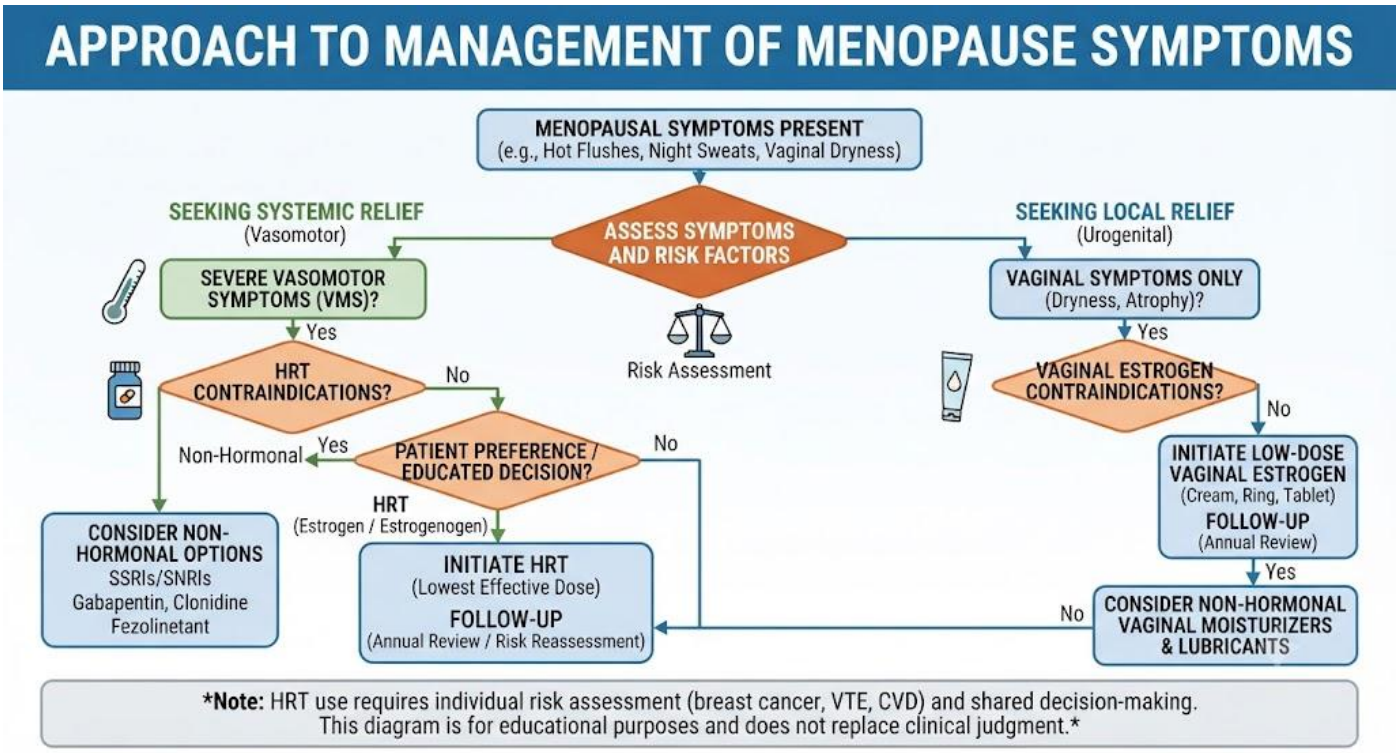

Figure 3.4: Approach to management of menopausal symptoms.

Pilot questions 3.4

1. Describe the indications for combined versus oestrogen-only hormone replacement therapy. (Linked to SLO 3.7)
2. Discuss the risks associated with hormone replacement therapy and how they inform prescribing decisions. (Linked to SLO 3.7)
3. Describe the non-hormonal options available for vasomotor symptoms. (Linked to SLO 3.7)
4. Describe the presentation and long-term risks of premature ovarian insufficiency. (Linked to SLO 3.8)
5. Discuss the management of premature ovarian insufficiency, including hormone replacement and psychological support. (Linked to SLO 3.8)

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Series Summary

This Series examined the climacteric and menopause, beginning with the physiology of ovarian decline and the characteristic rise in FSH and LH alongside falling oestradiol and inhibin B, and the staged nature of the menopausal transition. The range of vasomotor, urogenital and psychological symptoms was discussed alongside the long-term consequences of oestrogen deficiency for bone and cardiovascular health.

Diagnosis of menopause is generally clinical in women over 45 years, with hormonal testing reserved for younger women or unclear presentations, and important differentials such as thyroid dysfunction and pregnancy must be considered. Management centres on hormone replacement therapy, individualised against symptom severity and risk factors, with non-hormonal alternatives and lifestyle measures as important adjuncts, and premature ovarian insufficiency requiring particular attention given its greater cumulative health impact.

Glossary of Terms

1. **Climacteric:** the transitional phase of declining ovarian function surrounding menopause.
2. **Menopause:** the permanent cessation of menstruation, confirmed after twelve consecutive months of amenorrhoea.
3. **Perimenopause:** the period of irregular cycles and fluctuating hormone levels immediately surrounding menopause.
4. **Premature ovarian insufficiency:** menopause occurring before age 40.
5. **Early menopause:** menopause occurring between 40 and 45 years.
6. **Inhibin B:** a granulosa cell hormone that declines early in the menopausal transition.
7. **Vasomotor symptoms:** hot flushes and night sweats resulting from oestrogen withdrawal affecting hypothalamic thermoregulation.
8. **Genitourinary syndrome of menopause:** vaginal and urinary atrophic changes resulting from oestrogen deficiency.
9. **Osteoporosis:** reduced bone mineral density leading to increased fragility fracture risk, accelerated by oestrogen deficiency.
10. **STRAW staging:** a system for staging the menopausal transition based on menstrual and hormonal characteristics.
11. **Hormone replacement therapy:** treatment with oestrogen, with or without progestogen, to relieve menopausal symptoms and reduce long-term risk.

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12. **Endometrial hyperplasia:** abnormal thickening of the endometrium, a risk of unopposed oestrogen therapy in women with an intact uterus.

Concept Check Questions [Series 3]

Objective questions

- Menopause is confirmed after _____ consecutive months of amenorrhoea.
- Premature ovarian insufficiency is defined as menopause before age _____.
- _____ B is one of the earliest hormonal markers of diminishing ovarian reserve.
- Genitourinary syndrome of menopause results from thinning of the vaginal _____.
- Women with an intact uterus require combined oestrogen and _____ therapy.

Short-answer questions

1. Describe the hormonal changes in FSH, LH and oestradiol during the menopausal transition. (Linked to SLO 3.2)
2. Describe the vasomotor symptoms of menopause and their underlying mechanism. (Linked to SLO 3.4)
3. Describe the basis for clinical diagnosis of menopause in women over 45 years. (Linked to SLO 3.6)
4. Discuss the risks associated with hormone replacement therapy. (Linked to SLO 3.7)
5. Describe the presentation and long-term risks of premature ovarian insufficiency. (Linked to SLO 3.8)

Long-answer questions

6. Define the climacteric and menopause and describe the hormonal changes that occur across the transition. (Linked to SLO 3.1, SLO 3.2)
7. Discuss the perimenopausal and menopausal symptoms and their long-term health consequences. (Linked to SLO 3.4, SLO 3.5)

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8. Describe the clinical and hormonal approach to diagnosing menopause. (Linked to SLO 3.6)
9. Discuss the indications, types and risks of hormone replacement therapy. (Linked to SLO 3.7)
10. Describe the presentation and management of premature ovarian insufficiency. (Linked to SLO 3.8)

Answers to Concept Check Questions [Series 3]

Objective questions

11. Twelve.
12. 40.
13. Inhibin.
14. Epithelium.
15. Progestogen.

Short-answer questions

16. FSH and LH rise as oestradiol and inhibin B fall, reflecting progressive depletion of ovarian follicles and loss of negative feedback.
17. Hot flushes and night sweats result from oestrogen withdrawal narrowing the hypothalamic thermoregulatory zone, causing sudden heat and sweating episodes.
18. In women over 45 years with typical symptoms and menstrual irregularity progressing to amenorrhoea, diagnosis is clinical without routine hormonal testing.
19. Small increased risks of venous thromboembolism, particularly oral formulations, and, with longer combined use, a modest increase in breast cancer risk.
20. Menopause before age 40, with greater lifetime risk of osteoporosis and cardiovascular disease if untreated, alongside significant psychological impact.

Long-answer questions

21. **Basic response:** The climacteric is the transitional phase of ovarian decline; menopause is the permanent cessation of menstruation after twelve months of amenorrhoea, with FSH and LH rising as oestradiol and inhibin B fall.

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Value-added response: This staged hormonal decline, described by systems such as STRAW, underpins the gradual, rather than abrupt, nature of the symptoms most women experience.

22. **Basic response:** Vasomotor, urogenital and psychological symptoms are common, alongside long-term consequences including osteoporosis and increased cardiovascular risk from sustained oestrogen deficiency.

Value-added response: Recognising these long-term risks early supports timely discussion of hormone replacement therapy and lifestyle measures rather than addressing bone and cardiovascular health only after complications arise.

23. **Basic response:** Diagnosis is generally clinical in women over 45 years with typical symptoms; hormonal testing with FSH is reserved for younger women or unclear presentations.

Value-added response: Differentials such as thyroid dysfunction and pregnancy must be actively excluded rather than assumed, since both can mimic menopausal symptoms.

24. **Basic response:** Combined oestrogen and progestogen therapy is used with an intact uterus and oestrogen alone after hysterectomy, individualised by route, symptoms and risk factors.

Value-added response: The lowest effective dose for the shortest duration needed balances symptom control against small increased risks of thromboembolism and breast cancer.

25. **Basic response:** Premature ovarian insufficiency is menopause before age 40, presenting with amenorrhoea and menopausal symptoms and carrying greater lifetime health risk than natural menopause.

Value-added response: Hormone replacement is generally recommended until the average age of natural menopause, alongside fertility counselling and psychological support given the emotional impact of the diagnosis.

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Answers to Pilot Questions [Series 3]

Part 3.1

1. The climacteric is the transition of declining ovarian function; menopause is the permanent cessation of menstruation confirmed after twelve months of amenorrhoea.
2. Average age is around 51 years; premature ovarian insufficiency is menopause before 40, early menopause is between 40 and 45 years.
3. FSH and LH rise as follicle depletion removes negative feedback, while oestradiol falls progressively.
4. Inhibin B, from granulosa cells, declines early, often before FSH rises consistently, marking diminishing ovarian reserve.
5. Late reproductive stage, early and late menopausal transition, and early and late postmenopause, staged by menstrual and hormonal features.

Part 3.2

6. Sudden heat sensation with flushing and sweating, resulting from oestrogen withdrawal narrowing the hypothalamic thermoregulatory zone.
7. Night sweats disrupt sleep, contributing to fatigue and reduced quality of life during the transition.
8. Vaginal dryness, dyspareunia and urinary symptoms from atrophic changes due to declining oestrogen.
9. Mood lability, irritability and anxiety, often compounded by sleep disruption and midlife stressors, requiring careful history before attribution to menopause.
10. Accelerated bone loss and osteoporosis risk from increased osteoclast activity, and increased cardiovascular risk from loss of vascular protection.

Part 3.3

11. In women over 45 years with typical symptoms and menstrual irregularity, diagnosis is generally clinical without routine testing.
12. Suspected premature ovarian insufficiency under 40, symptomatic women 40 to 45 years, and unclear presentations such as after hysterectomy.
13. Persistently elevated FSH above 25 to 30 IU/L on two occasions with low oestradiol supports the diagnosis.

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14. Thyroid dysfunction can cause menstrual irregularity, flushing and mood disturbance and should be excluded when symptoms are atypical.
15. Ovulation can occur intermittently during the perimenopause, so pregnancy must always be excluded before attributing amenorrhoea to menopause.

Part 3.4

1. Combined oestrogen and progestogen is used with an intact uterus to protect the endometrium; oestrogen alone is used after hysterectomy.
2. Small increased risk of venous thromboembolism, particularly with oral formulations, and modest increased breast cancer risk with longer combined use.
3. SSRIs, SNRIs, gabapentin and clonidine, generally less effective than HRT and selected by contraindications and symptom profile.
4. Amenorrhoea and menopausal symptoms before age 40, with greater lifetime risk of osteoporosis and cardiovascular disease if untreated.
5. HRT is generally recommended until the average age of natural menopause, alongside fertility counselling and psychological support.

References and Attributions [Series 3]

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4. Berek, J. S. and Berek, D. L. (2019). Berek and Novak's Gynecology (16th ed.). Wolters Kluwer.

Figures, Plates, Tables, and Boxes

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1. **Figure 3.1**: Hormonal changes across the menopausal transition. AI-generated using the prompt: "Create a clean line graph titled Hormonal Changes Across the Menopausal Transition, showing FSH, LH, oestradiol and inhibin B trends. Clinical educational diagram style."
2. **Table 3.2**: Perimenopausal and menopausal symptoms by system. AI-generated using the prompt: "Create a clean reference table titled Perimenopausal and Menopausal Symptoms by System, organised by body system. Simple clinical reference table style with outside border."
3. **Box 3.3**: Indications for hormonal testing in suspected menopause. AI-generated using the prompt: "Create a simple single-column reference box titled Indications for Hormonal Testing in Suspected Menopause, listing key clinical situations. Clean clinical reference box style."
4. **Figure 3.4**: Approach to management of menopausal symptoms. AI-generated using the prompt: "Create a professional medical flowchart titled Approach to Management of Menopausal Symptoms, showing decision points for HRT versus non-hormonal treatment. Clean clinical educational diagram style."

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Course code: OBG 514

Course title: Reproductive Endocrinology and Fertility

Course credit load: 2 Units

Series 4: Sexuality and Dysfunction

- **Part 4.1: Physiology of Human Sexual Response**
  - Sub Part 4.1.1: Anatomy and physiology of coitus
  - Sub Part 4.1.2: The sexual response cycle
  - Sub Part 4.1.3: Hormonal and neurological control of sexual function
- **Part 4.2: Female Sexual Dysfunction**
  - Sub Part 4.2.1: Classification of female sexual dysfunction
  - Sub Part 4.2.2: Causes of female sexual dysfunction
  - Sub Part 4.2.3: Evaluation and management of female sexual dysfunction
- **Part 4.3: Male Sexual Dysfunction**
  - Sub Part 4.3.1: Erectile dysfunction
  - Sub Part 4.3.2: Ejaculatory disorders
  - Sub Part 4.3.3: Evaluation and management of male sexual dysfunction
- **Part 4.4: Rape and Sexual Violence**
  - Sub Part 4.4.1: Definition and medico-legal aspects of rape
  - Sub Part 4.4.2: Clinical management of the rape survivor
  - Sub Part 4.4.3: Psychological support and prevention

Introduction

In the last Series, we explored the climacteric and menopause, understanding the hormonal transition that affects women in midlife. We now turn to human sexuality and its disorders, a topic that spans normal physiology, the dysfunctions that can affect both women and men, and the medico-legal dimension of sexual violence.

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Sexual function depends on an intact interplay of vascular, neurological, hormonal and psychological factors, and disruption at any level can result in dysfunction that affects quality of life and relationships. Rape, by contrast, is not a disorder of sexual function but an act of violence, and its clinical management requires a distinct, survivor-centred approach.

This Series covers the physiology of human sexual response, the classification, causes and management of female and male sexual dysfunction, and the definition, clinical management and psychological support relevant to rape and sexual violence.

Series Learning Outcomes

Upon completing this Series, you should be able to:

- **SLO 4.1:** describe the physiology of coitus and the human sexual response cycle,
- **SLO 4.2:** describe the hormonal and neurological control of sexual function,
- **SLO 4.3:** classify and describe the causes of female sexual dysfunction,
- **SLO 4.4:** describe the evaluation and management of female sexual dysfunction,
- **SLO 4.5:** describe the causes and classification of male sexual dysfunction,
- **SLO 4.6:** describe the evaluation and management of male sexual dysfunction,
- **SLO 4.7:** define rape and discuss its medico-legal aspects, and
- **SLO 4.8:** describe the clinical and psychological management of the rape survivor.

Part 4.1: Physiology of Human Sexual Response

4.1.1 Anatomy and physiology of coitus

Coitus involves coordinated vascular, muscular and neurological events in both partners, beginning with genital vasocongestion driven by parasympathetic activation, which produces vaginal lubrication and lengthening in women and penile erection in men, followed by rhythmic pelvic movement culminating in orgasm and, in men, ejaculation.

Adequate lubrication and vaginal expansion depend on intact vascular supply and oestrogen-dependent tissue integrity, meaning conditions that impair pelvic blood flow or reduce oestrogen

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levels, such as menopause, can directly affect the physical comfort and function of coitus, independent of any psychological factor.

Fill in the blank: Genital vasocongestion during arousal is driven by _____ activation. Adequate vaginal lubrication depends on intact vascular supply and _____-dependent tissue integrity.

4.1.2 The sexual response cycle

The sexual response cycle is classically described in four phases: excitement, marked by rising arousal and genital vasocongestion; plateau, a sustained heightened state preceding climax; orgasm, the brief, intense peak involving rhythmic muscular contraction; and resolution, during which the body returns to its unaroused baseline state.

Desire is now widely recognised as a distinct component preceding or interwoven with excitement, and modern models emphasise that arousal and desire can be responsive to context and stimuli rather than always spontaneous, a distinction that is particularly relevant to understanding female sexual response and its disorders.

Fill in the blank: The four classical phases of sexual response are excitement, plateau, _____, and resolution. _____ is now recognised as a distinct component preceding or interwoven with excitement.

4.1.3 Hormonal and neurological control of sexual function

Testosterone is the principal hormone underlying sexual desire in both sexes, produced in much larger amounts by the testes in men but also contributing meaningfully to libido in women through ovarian and adrenal production, meaning conditions or treatments that lower testosterone can reduce desire in either sex.

The autonomic nervous system governs the physical response: parasympathetic activation produces vasocongestion, lubrication and erection, while sympathetic activation drives orgasm and ejaculation, meaning conditions or medications that disrupt autonomic function, such as diabetes mellitus or certain antidepressants, can impair sexual response at a physiological level.

Fill in the blank: _____ is the principal hormone underlying sexual desire in both sexes. _____ activation of the autonomic nervous system produces vasocongestion, lubrication and erection.

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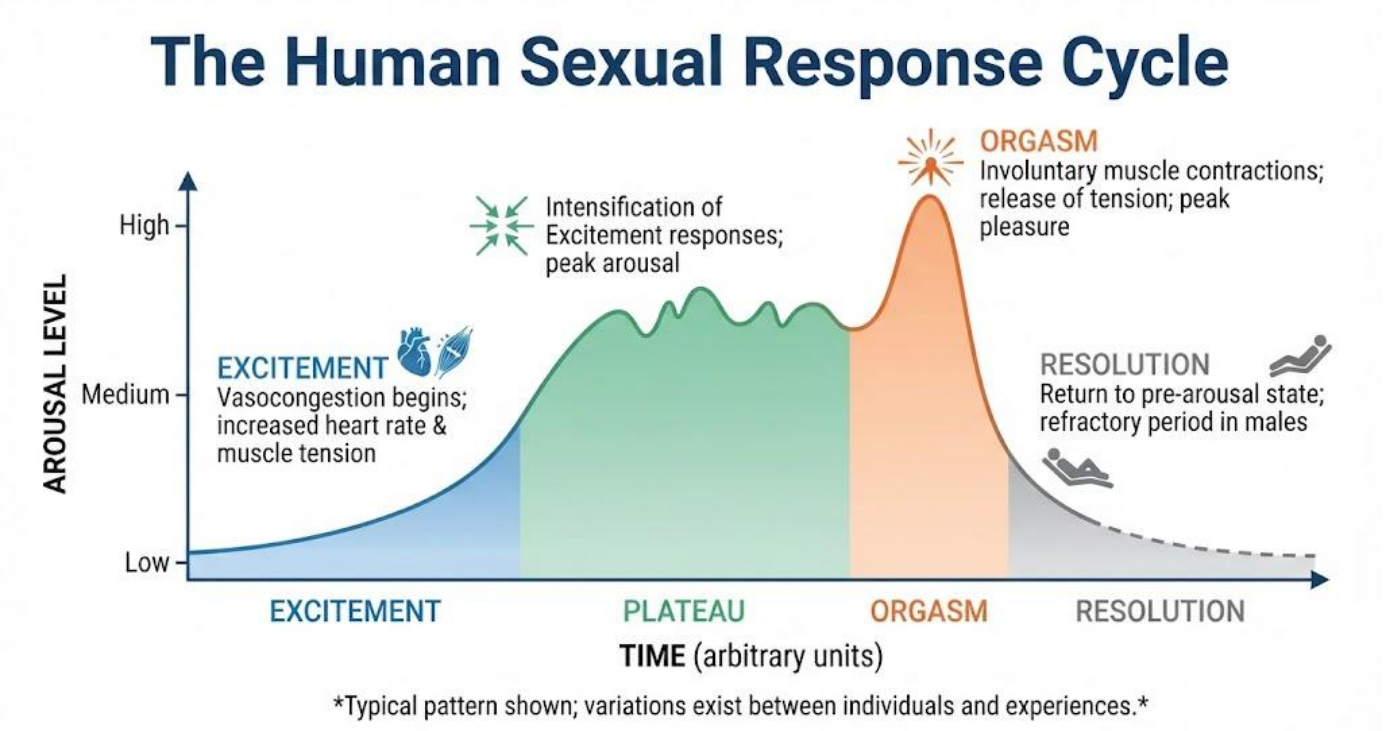

Figure 4.1: The four phases of the human sexual response cycle.

Pilot questions 4.1

1. Describe the vascular and neurological events of coitus in both sexes. (Linked to SLO 4.1)
2. Explain why oestrogen deficiency can directly affect the physical comfort of coitus. (Linked to SLO 4.1)
3. Describe the four phases of the classical sexual response cycle. (Linked to SLO 4.1)
4. Discuss the role of testosterone in sexual desire in both sexes. (Linked to SLO 4.2)
5. Describe the roles of parasympathetic and sympathetic activation in sexual response. (Linked to SLO 4.2)

Part 4.2: Female Sexual Dysfunction

4.2.1 Classification of female sexual dysfunction

Female sexual dysfunction is classified into disorders of desire and arousal, now often combined given their overlap, orgasmic disorder, characterised by absent, delayed or diminished orgasm, and genito-pelvic pain and penetration disorder, encompassing dyspareunia and

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vaginismus, with a diagnosis generally requiring the difficulty to be persistent and to cause personal distress.

The distress criterion is central to diagnosis, since low desire or infrequent orgasm without accompanying distress is not itself classified as dysfunction, reflecting a shift toward recognising considerable normal variation in sexual response rather than pathologising it.

Fill in the blank: Female sexual dysfunction includes desire and arousal disorder, orgasmic disorder, and genito-pelvic pain and _____ disorder. Diagnosis generally requires accompanying personal _____.

4.2.2 Causes of female sexual dysfunction

Causes of female sexual dysfunction span biological factors, including hormonal deficiency at menopause, vascular disease, chronic illness, medication side effects, particularly certain antidepressants, and pelvic pathology such as endometriosis, alongside psychological factors including anxiety, depression, body image concerns, and relationship or interpersonal difficulty.

Vaginismus specifically involves involuntary spasm of the pelvic floor muscles surrounding the vagina, making penetration painful or impossible, and often has both physical and psychological contributing factors, including anticipatory fear following a prior painful experience or trauma.

Fill in the blank: Causes of female sexual dysfunction include hormonal deficiency, vascular disease, and certain _____ side effects. _____ involves involuntary spasm of the pelvic floor muscles surrounding the vagina.

4.2.3 Evaluation and management of female sexual dysfunction

Evaluation requires a sensitive, detailed sexual and psychosocial history, alongside examination to identify any physical contributing cause, and appropriate investigation directed by findings, such as hormonal testing where hypoestrogenism is suspected or assessment for pelvic pathology where pain is the presenting complaint.

Management is directed at the identified cause and may include topical or systemic oestrogen for genitourinary atrophy, pelvic floor physiotherapy for vaginismus, psychosexual counselling or couples therapy, and treatment or adjustment of any contributing medication, with combined biological and psychological approaches often most effective.

Fill in the blank: Management of hypoestrogenism-related dysfunction may include topical or systemic _____. Vaginismus is often managed with pelvic floor _____.

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Category	Common Causes
Desire Disorders	Hormonal changes (estrogen/testosterone deficiency), chronic illness, medications (antidepressants, antihypertensives), psychological stress, relationship issues
Arousal Disorders	Vascular insufficiency, neurological impairment, diabetes, pelvic surgery, medications, anxiety
Orgasmic Disorders	Psychological factors, inadequate stimulation, antidepressant use (SSRIs), pelvic nerve damage
Pain Disorders	Vaginal dryness (menopause), vulvodynia, endometriosis, pelvic inflammatory disease, infections, trauma, inadequate lubrication

Table 4.2: Classification and causes of female sexual dysfunction.

Pilot questions 4.2

1. Classify female sexual dysfunction and explain the role of the distress criterion in diagnosis. (Linked to SLO 4.3)
2. Describe the biological causes of female sexual dysfunction. (Linked to SLO 4.3)
3. Describe vaginismus and its contributing factors. (Linked to SLO 4.3)
4. Describe the evaluation of a woman presenting with female sexual dysfunction. (Linked to SLO 4.4)
5. Discuss the management options for female sexual dysfunction. (Linked to SLO 4.4)

Part 4.3: Male Sexual Dysfunction

4.3.1 Erectile dysfunction

Erectile dysfunction is the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance, and becomes increasingly common with age, with vascular disease being the most common underlying cause given the shared risk factors of diabetes mellitus, hypertension and smoking with cardiovascular disease generally.

Erectile dysfunction can be an early marker of underlying cardiovascular disease, since the small penile arteries are affected by atherosclerosis before larger coronary vessels, meaning new

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erectile dysfunction in a man without an obvious psychological cause warrants cardiovascular risk assessment.

Fill in the blank: Vascular disease is the most common underlying cause of _____ dysfunction. Erectile dysfunction can be an early marker of underlying _____ disease.

4.3.2 Ejaculatory disorders

Premature ejaculation is the most common male ejaculatory disorder, defined as ejaculation occurring sooner than desired, generally within about a minute of penetration, causing distress, and may be lifelong or acquired, the latter often associated with anxiety, relationship difficulty, or an underlying prostate or urological condition.

Delayed ejaculation and anejaculation are less common and may result from certain medications, particularly selective serotonin reuptake inhibitors, neurological conditions affecting the pelvic nerves, or psychological factors, with careful history distinguishing lifelong from acquired presentations to guide the search for an underlying cause.

Fill in the blank: Premature ejaculation generally occurs within about a _____ of penetration. Delayed ejaculation may result from certain medications, particularly _____.

4.3.3 Evaluation and management of male sexual dysfunction

Evaluation includes a detailed sexual, medical and medication history, examination for signs of hypogonadism or vascular disease, and targeted investigation including testosterone level, fasting glucose and lipid profile given the shared risk factors with cardiovascular disease.

Management of erectile dysfunction includes phosphodiesterase type 5 inhibitors as first-line pharmacological treatment, lifestyle modification addressing shared cardiovascular risk factors, and psychosexual counselling where a psychological contributor is identified, while premature ejaculation may be managed with behavioural techniques, topical anaesthetic agents, or selective serotonin reuptake inhibitors.

Fill in the blank: Phosphodiesterase type 5 inhibitors are first-line pharmacological treatment for _____ dysfunction. Evaluation should include testosterone level, fasting glucose, and _____ profile.

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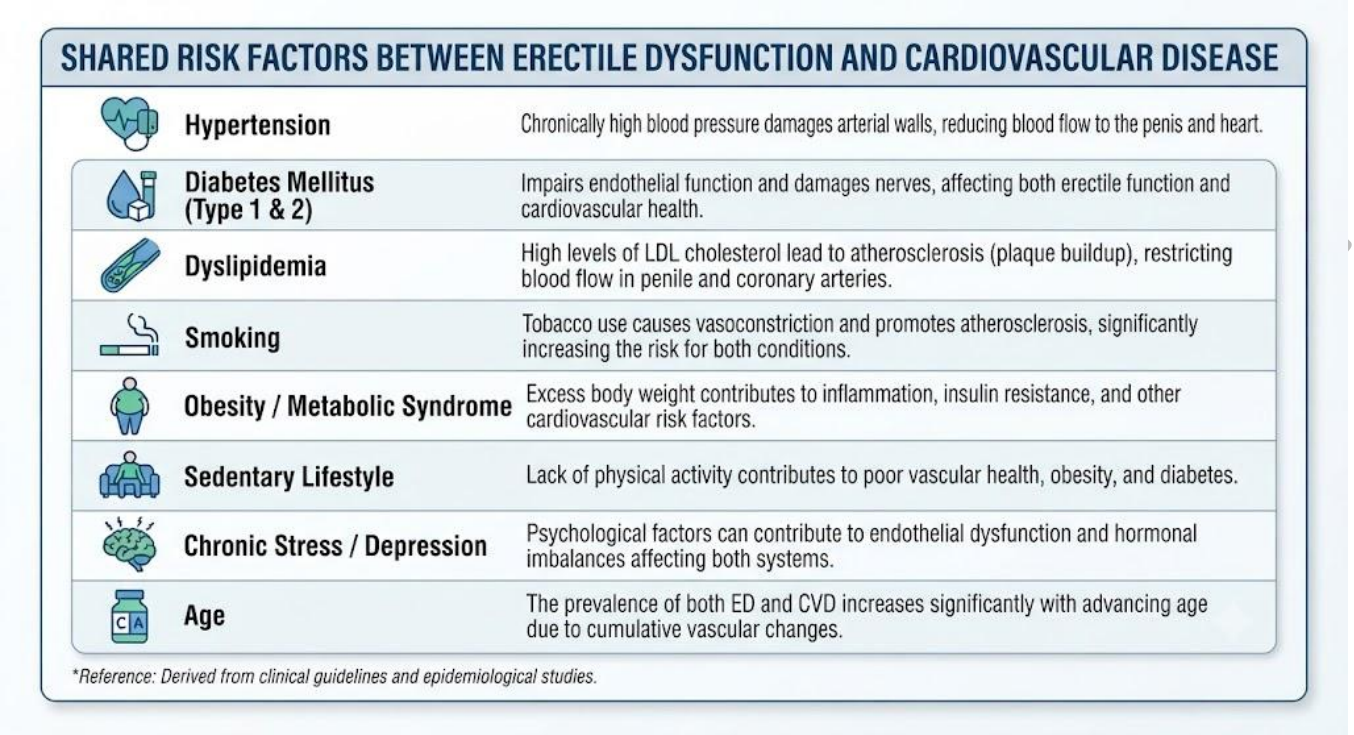

Box 4.3: Shared risk factors between erectile dysfunction and cardiovascular disease.

Pilot questions 4.3

1. Define erectile dysfunction and describe its most common underlying cause. (Linked to SLO 4.5)
2. Explain why erectile dysfunction can be an early marker of cardiovascular disease. (Linked to SLO 4.5)
3. Describe premature ejaculation and distinguish lifelong from acquired presentations. (Linked to SLO 4.5)
4. Describe the evaluation of a man presenting with erectile dysfunction. (Linked to SLO 4.6)
5. Discuss the management options for erectile dysfunction and premature ejaculation. (Linked to SLO 4.6)

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Part 4.4: Rape and Sexual Violence

4.4.1 Definition and medico-legal aspects of rape

Rape is defined as sexual penetration occurring without valid consent, whether achieved through force, threat, incapacitation, or exploitation of a person unable to give consent, and constitutes both a serious crime and a medical emergency requiring urgent, sensitive clinical attention.

The medico-legal role of the clinician includes careful, contemporaneous documentation of history and examination findings, collection of forensic evidence with proper chain of custody where the survivor consents, and provision of a medical report that may later be required for legal proceedings, all conducted without judgement or assumption about the survivor's account.

Fill in the blank: Rape is sexual penetration occurring without valid _____. Forensic evidence must be collected with proper chain of _____ where the survivor consents.

4.4.2 Clinical management of the rape survivor

Immediate clinical management includes attention to any injury requiring treatment, assessment and prevention of pregnancy through emergency contraception where appropriate, and post-exposure prophylaxis against sexually transmitted infections, including HIV, ideally commenced within 72 hours of the assault for maximum effectiveness.

A survivor-centred approach means the survivor retains control over each step of the examination and any forensic evidence collection, with informed consent obtained for every component, since restoring a sense of control is itself an important part of supporting recovery after an experience defined by its loss.

Fill in the blank: Post-exposure prophylaxis against HIV is ideally commenced within _____ hours of the assault. A _____-centred approach means the survivor retains control over each step of the examination.

4.4.3 Psychological support and prevention

Psychological support is an essential and ongoing component of care, since survivors commonly experience acute distress, and some go on to develop longer-term conditions such as post-traumatic stress disorder, meaning referral to counselling services and follow-up support should be offered as a routine part of management rather than only when specifically requested.

Prevention efforts operate at multiple levels, including community education challenging attitudes that enable sexual violence, support for survivors that encourages reporting, and health system readiness through trained personnel and clear protocols, all of which are relevant to reducing the burden of sexual violence at a population level.

Fill in the blank: Some survivors go on to develop longer-term conditions such as post-traumatic stress _____. Prevention efforts include community education challenging attitudes that enable sexual _____.

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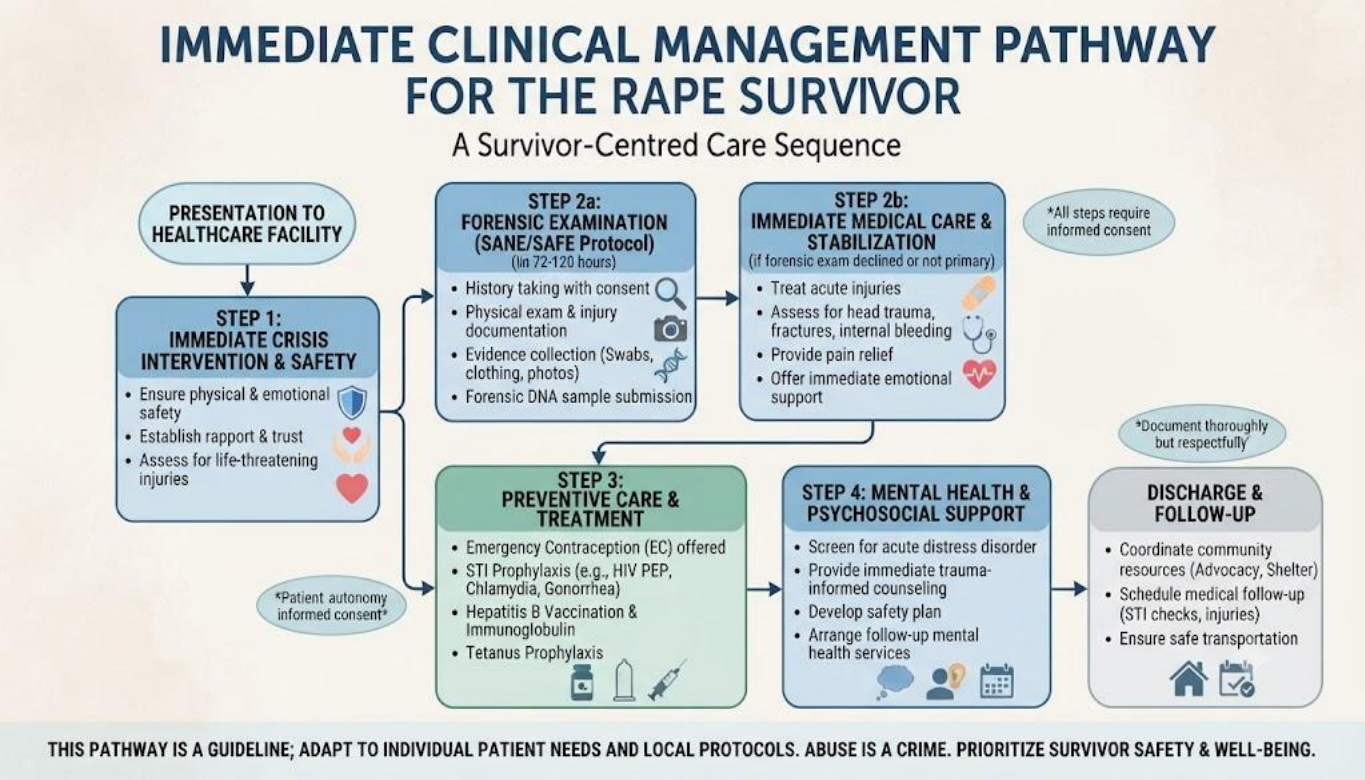

Figure 4.4: Immediate clinical management pathway for the rape survivor.

Pilot questions 4.4

1. Define rape and describe the medico-legal responsibilities of the examining clinician. (Linked to SLO 4.7)
2. Describe the immediate clinical priorities in managing a rape survivor. (Linked to SLO 4.8)
3. Explain the timing and rationale for post-exposure HIV prophylaxis after sexual assault. (Linked to SLO 4.8)
4. Explain what is meant by a survivor-centred approach to examination and evidence collection. (Linked to SLO 4.8)
5. Discuss the psychological support needs of rape survivors and approaches to prevention. (Linked to SLO 4.8)

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Series Summary

This Series examined human sexuality and its disorders, beginning with the physiology of coitus and the sexual response cycle, and the hormonal and neurological control underlying normal function. Female sexual dysfunction was classified into desire and arousal, orgasmic, and genito-pelvic pain and penetration disorders, with causes spanning biological and psychological factors and management combining both approaches.

Male sexual dysfunction was examined through erectile dysfunction and ejaculatory disorders, highlighting the important link between erectile dysfunction and cardiovascular disease. Finally, rape and sexual violence were addressed as a medical emergency requiring survivor-centred clinical management, medico-legal documentation, and ongoing psychological support, alongside multi-level prevention efforts.

Glossary of Terms

- **Coitus:** sexual intercourse involving coordinated vascular, muscular and neurological events.
- **Sexual response cycle:** the classical four-phase model of excitement, plateau, orgasm and resolution.
- **Female sexual dysfunction:** a persistent, distressing disturbance of desire, arousal, orgasm, or genito-pelvic comfort.
- **Vaginismus:** involuntary spasm of the pelvic floor muscles surrounding the vagina, making penetration painful or impossible.
- **Dyspareunia:** persistent or recurrent pain associated with sexual intercourse.
- **Erectile dysfunction:** the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance.
- **Premature ejaculation:** ejaculation occurring sooner than desired, generally within about a minute of penetration, causing distress.
- **Phosphodiesterase type 5 inhibitor:** a class of drug used as first-line pharmacological treatment for erectile dysfunction.
- **Rape:** sexual penetration occurring without valid consent.
- **Post-exposure prophylaxis:** medication given after potential exposure to prevent infection, including HIV after sexual assault.

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- **Survivor-centred approach:** an approach to care in which the survivor retains control over each step of examination and evidence collection.
- **Post-traumatic stress disorder:** a psychological condition that can develop following a traumatic experience such as sexual assault.

Concept Check Questions [Series 4]

Objective questions

1. Genital vasocongestion during arousal is driven by _____ activation.
2. The four classical phases of sexual response are excitement, plateau, _____, and resolution.
3. Vaginismus involves involuntary spasm of the _____ muscles surrounding the vagina.
4. Vascular disease is the most common underlying cause of _____ dysfunction.
5. Rape is sexual penetration occurring without valid _____.

Short-answer questions

6. Describe the four phases of the classical sexual response cycle. (Linked to SLO 4.1)
7. Describe the biological and psychological causes of female sexual dysfunction. (Linked to SLO 4.3)
8. Explain why erectile dysfunction can be an early marker of cardiovascular disease. (Linked to SLO 4.5)
9. Describe the immediate clinical priorities in managing a rape survivor. (Linked to SLO 4.8)
10. Explain what is meant by a survivor-centred approach to examination. (Linked to SLO 4.8)

Long-answer questions

11. Describe the physiology of coitus and the sexual response cycle, including its hormonal and neurological control. (Linked to SLO 4.1, SLO 4.2)

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12. Classify female sexual dysfunction, discuss its causes, and describe its evaluation and management. (Linked to SLO 4.3, SLO 4.4)
13. Describe the causes, evaluation and management of erectile dysfunction and ejaculatory disorders in men. (Linked to SLO 4.5, SLO 4.6)
14. Define rape and discuss the medico-legal aspects relevant to the examining clinician. (Linked to SLO 4.7)
15. Describe the clinical and psychological management of the rape survivor, including prevention efforts. (Linked to SLO 4.8)

Answers to Concept Check Questions [Series 4]

Objective questions

1. Parasympathetic.
2. Orgasm.
3. Pelvic floor.
4. Erectile.
5. Consent.

Short-answer questions

6. Excitement with rising arousal and vasocongestion, plateau as a sustained heightened state, orgasm as the brief intense peak, and resolution returning to baseline.
7. Biological causes include hormonal deficiency, vascular disease and medication effects; psychological causes include anxiety, depression and relationship difficulty; both often coexist.
8. The small penile arteries are affected by atherosclerosis before larger coronary vessels, so erectile dysfunction can precede overt cardiovascular disease.
9. Attention to injury, pregnancy prevention through emergency contraception, and post-exposure prophylaxis against sexually transmitted infections including HIV.
10. The survivor retains control over each step of the examination and evidence collection, with informed consent obtained for every component.

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Long-answer questions

11. **Basic response:** Coitus involves coordinated vasocongestion and muscular response through parasympathetic and sympathetic activation, progressing through excitement, plateau, orgasm and resolution, with testosterone underlying desire in both sexes.

Value-added response: Recognising desire as responsive rather than only spontaneous is particularly relevant to understanding normal variation in female sexual response.

12. **Basic response:** Female sexual dysfunction is classified into desire and arousal, orgasmic, and genito-pelvic pain and penetration disorders, caused by biological and psychological factors, and managed with a combined approach directed at the identified cause.

Value-added response: The distress criterion is central, since normal variation in desire or orgasm without distress is not itself classified as dysfunction.

13. **Basic response:** Erectile dysfunction is most commonly vascular in origin and evaluated with attention to cardiovascular risk factors; ejaculatory disorders include premature and delayed ejaculation, each with distinct causes and management.

Value-added response: Because erectile dysfunction can be an early marker of cardiovascular disease, evaluation should extend beyond sexual history to cardiovascular risk assessment.

14. **Basic response:** Rape is sexual penetration without valid consent; the clinician's medico-legal role includes careful documentation and forensic evidence collection with proper chain of custody.

Value-added response: This documentation must be conducted without judgement, since it may later be required to support legal proceedings on the survivor's behalf.

15. **Basic response:** Management includes injury care, pregnancy and infection prevention, and psychological referral, delivered through a survivor-centred approach that restores control.

Value-added response: Prevention operates at multiple levels, including community education, survivor support, and health system readiness, extending care beyond the individual encounter.

Answers to Pilot Questions [Series 4]

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Part 4.1

6. Parasympathetic activation produces vasocongestion, lubrication and erection; sympathetic activation drives orgasm and ejaculation.
7. Oestrogen deficiency reduces vascular supply and tissue integrity needed for lubrication and vaginal expansion, directly affecting comfort during coitus.
8. Excitement, plateau, orgasm, and resolution.
9. Testosterone underlies desire in both sexes, produced predominantly by the testes in men and by the ovaries and adrenals in women.
10. Parasympathetic activation produces the physical arousal response; sympathetic activation drives orgasm and ejaculation.

Part 4.2

11. Desire and arousal disorder, orgasmic disorder, and genito-pelvic pain and penetration disorder, each requiring accompanying personal distress for diagnosis.
12. Hormonal deficiency, vascular disease, chronic illness, and medication side effects, particularly certain antidepressants.
13. Involuntary pelvic floor muscle spasm making penetration painful or impossible, often with both physical and psychological contributing factors.
14. A sensitive sexual and psychosocial history, examination for physical causes, and investigation directed by findings, such as hormonal testing.
15. Topical or systemic oestrogen, pelvic floor physiotherapy, psychosexual counselling, and adjustment of contributing medication.

Part 4.3

1. Persistent inability to achieve or maintain a satisfactory erection, most commonly due to vascular disease sharing risk factors with cardiovascular disease.
2. Small penile arteries are affected by atherosclerosis before larger coronary vessels, so erectile dysfunction can be an early warning sign.
3. Ejaculation within about a minute of penetration causing distress; lifelong presentations begin with first sexual experience, acquired presentations develop later.
4. Sexual, medical and medication history, examination for hypogonadism or vascular disease, and testosterone, glucose and lipid testing.

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5. Phosphodiesterase type 5 inhibitors and lifestyle modification for erectile dysfunction; behavioural techniques or SSRIs for premature ejaculation.

Part 4.4

1. Sexual penetration without valid consent; the clinician documents findings carefully and collects forensic evidence with proper chain of custody.
2. Treatment of injury, emergency contraception where appropriate, and post-exposure prophylaxis against sexually transmitted infections including HIV.
3. Ideally within 72 hours of assault, since prophylaxis is most effective when commenced promptly after potential exposure.
4. The survivor retains control over each step of the examination and evidence collection, with informed consent obtained throughout.
5. Referral to counselling given the risk of post-traumatic stress disorder, alongside community education and health system readiness for prevention.

References and Attributions [Series 4]

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3. World Health Organization (2013). Guidelines for Medico-Legal Care for Victims of Sexual Violence.
4. Berek, J. S. and Berek, D. L. (2019). Berek and Novak's Gynecology (16th ed.). Wolters Kluwer.

Figures, Plates, Tables, and Boxes

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1. Figure 4.1: The four phases of the human sexual response cycle. AI-generated using the prompt: "Create a clean line graph titled The Human Sexual Response Cycle, showing arousal level across four phases. Clinical educational diagram style."
2. Table 4.2: Classification and causes of female sexual dysfunction. AI-generated using the prompt: "Create a clean reference table titled Classification and Causes of Female Sexual Dysfunction, organised by category. Simple clinical reference table style with outside border."
3. Box 4.3: Shared risk factors between erectile dysfunction and cardiovascular disease. AI-generated using the prompt: "Create a simple single-column reference box titled Shared Risk Factors Between Erectile Dysfunction and Cardiovascular Disease. Clean clinical reference box style."
4. Figure 4.4: Immediate clinical management pathway for the rape survivor. AI-generated using the prompt: "Create a professional medical flowchart titled Immediate Clinical Management Pathway for the Rape Survivor, showing a survivor-centred care sequence. Clean, respectful clinical educational diagram style."

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Course code: OBG 514

Course title: Reproductive Endocrinology and Fertility

Course credit load: 2 Units

Series 5: Infertility and Assisted Reproduction

- **Part 5.1: Overview and Epidemiology of Infertility**
  - Sub Part 5.1.1: Definition and classification of infertility
  - Sub Part 5.1.2: Epidemiology of infertility
  - Sub Part 5.1.3: Causes of female infertility
- **Part 5.2: Male Infertility**
  - Sub Part 5.2.1: Causes of male infertility
  - Sub Part 5.2.2: Evaluation of male infertility
  - Sub Part 5.2.3: Management of male infertility
- **Part 5.3: Investigation of the Infertile Couple**
  - Sub Part 5.3.1: History and examination
  - Sub Part 5.3.2: Ovulation and tubal patency assessment
  - Sub Part 5.3.3: Semen analysis and further investigations
- **Part 5.4: Assisted Reproductive Techniques**
  - Sub Part 5.4.1: Ovulation induction and intrauterine insemination
  - Sub Part 5.4.2: In vitro fertilisation
  - Sub Part 5.4.3: Other techniques and ethical considerations

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Introduction

In the last Series, we explored **human sexuality** and its disorders, including **female sexual dysfunction**, **male sexual dysfunction**, and the clinical management of **rape and sexual**

violence. We now turn to **infertility**, one of the most emotionally significant presentations in reproductive medicine, affecting couples across every social and economic background and carrying substantial psychological, social, and, in many settings, cultural weight, particularly in societies such as Nigeria where childbearing carries strong social expectation.

Infertility may originate from the female partner, the male partner, both partners together, or remain **unexplained** despite thorough investigation, meaning a systematic, couple-centred approach to evaluation is essential rather than assuming the cause lies with either partner alone. Advances in **assisted reproductive technology**, including **ovulation induction**, **intrauterine insemination**, and **in vitro fertilisation**, have transformed the prospects for many couples who would previously have had no realistic chance of conceiving.

This Series covers the definition, classification, and **epidemiology of infertility**, the causes and evaluation of **male infertility**, the systematic investigation of the infertile couple, and the principal **assisted reproductive techniques** available, alongside the ethical considerations that accompany them.

Series Learning Outcomes

Upon completing this Series, you should be able to:

- **SLO 5.1:** define infertility and classify primary and secondary infertility,
- **SLO 5.2:** describe the epidemiology of infertility,
- **SLO 5.3:** enumerate the causes of female infertility,
- **SLO 5.4:** describe the causes and evaluation of male infertility,
- **SLO 5.5:** describe the management of male infertility,
- **SLO 5.6:** describe the systematic investigation of the infertile couple,
- **SLO 5.7:** describe the principles of ovulation induction and intrauterine insemination, and
- **SLO 5.8:** describe the process and ethical considerations of in vitro fertilisation.

Part 5.1: Overview and Epidemiology of Infertility

5.1.1 Definition and classification of infertility

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Infertility is defined as the inability to conceive after twelve months of regular, unprotected intercourse, and is classified as **primary infertility**, where the woman has never conceived, or **secondary infertility**, where conception has occurred previously, whether or not that pregnancy resulted in a live birth. **Subfertility** is sometimes used interchangeably, though it more precisely describes reduced, rather than absent, fertility, and couples presenting after a shorter interval, particularly women approaching or beyond 35 years, are generally offered earlier evaluation given the more limited window for successful treatment.

The distinction between **primary** and **secondary infertility** carries genuine clinical relevance, since secondary infertility raises specific possibilities such as **tubal damage** from a previous pregnancy complication or delivery, or **acquired pelvic infection**, that would not apply to a woman who has never conceived, meaning the history of any previous pregnancy, its outcome, and any associated complications should always be carefully explored during assessment.

Fill in the blank: Infertility is defined as inability to conceive after _____ months of regular unprotected intercourse. _____ infertility describes a woman who has conceived before, regardless of outcome.

5.1.2 Epidemiology of infertility

Infertility affects an estimated one in six couples globally at some point during their reproductive lives, with rates varying by region and influenced by factors including **age**, **sexually transmitted infection prevalence**, and access to reproductive healthcare. In many parts of **sub-Saharan Africa**, including **Nigeria**, rates of **secondary infertility** are notably elevated, frequently linked to **untreated pelvic infection** following childbirth, unsafe abortion, or **sexually transmitted infection**, particularly **gonorrhoea** and **chlamydia**, which can cause **tubal damage** without ever being clinically recognised or treated.

The burden of infertility extends well beyond the biological, encompassing significant **psychological distress**, **marital strain**, and, in many Nigerian communities, considerable **social stigma** disproportionately directed at women regardless of where the underlying cause actually lies, underscoring the importance of a compassionate, non-judgemental approach and, where relevant, involving both partners equally in counselling and investigation from the outset.

Fill in the blank: An estimated one in _____ couples globally experience infertility. Secondary infertility in Nigeria is frequently linked to untreated _____ infection following childbirth or unsafe abortion.

5.1.3 Causes of female infertility

Female infertility arises from several principal categories: **ovulatory disorders**, including **polycystic ovarian syndrome** and **premature ovarian insufficiency**, accounting for a substantial proportion of cases; **tubal factor infertility**, most commonly resulting from **pelvic inflammatory disease**; **uterine factors**, such as **fibroids** or **congenital anomalies** distorting the uterine cavity; and **endometriosis**, which can impair fertility through both anatomical distortion and inflammatory effects on the pelvic environment.

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Cervical factors, including **cervical stenosis** or hostile cervical mucus, and **unexplained infertility**, where no cause is identified despite thorough investigation of both partners, account for the remainder of cases, with unexplained infertility representing a genuinely important category since it neither confirms nor excludes a subtle contributing factor in either partner that available investigations simply cannot detect.

Fill in the blank: _____ disorders, including PCOS, account for a substantial proportion of female infertility cases. _____ factor infertility most commonly results from pelvic inflammatory disease.

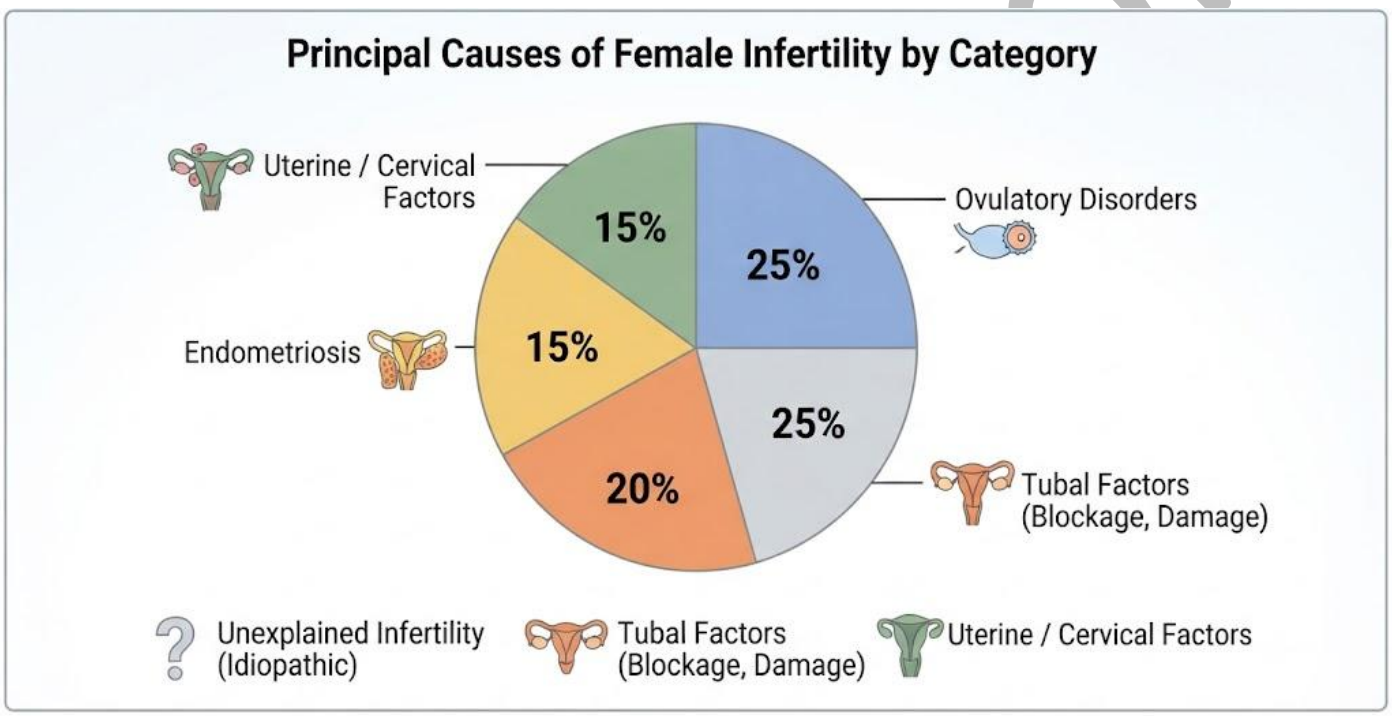

Figure 5.1: Principal causes of female infertility by category.

Figure 5.1: Principal causes of female infertility by category.

Pilot questions 5.1

1. Define infertility and distinguish primary from secondary infertility. (Linked to SLO 5.1)
2. Explain why women approaching or beyond 35 years are generally offered earlier evaluation. (Linked to SLO 5.1)
3. Describe the global epidemiology of infertility and the factors that influence regional variation. (Linked to SLO 5.2)
4. Discuss the particular burden of secondary infertility in Nigeria and its common causes. (Linked to SLO 5.2)

5. Enumerate the principal causes of female infertility. (Linked to SLO 5.3)

Part 5.2: Male Infertility

5.2.1 Causes of male infertility

Male infertility contributes to roughly half of all infertility cases, either alone or alongside a female factor, and arises from three broad categories: **pre-testicular causes**, including **hypogonadotropic hypogonadism** reducing gonadotropin stimulation of the testes; **testicular causes**, such as **varicocele**, the most common surgically correctable cause, **cryptorchidism**, **mumps orchitis**, and **genetic conditions** including **Klinefelter syndrome**; and **post-testicular causes**, including **obstruction** of the reproductive tract, **infection**, and **erectile or ejaculatory dysfunction** impairing sperm delivery despite normal production.

Varicocele, an abnormal dilation of the veins draining the testis, is thought to impair fertility through increased **scrotal temperature** and localised venous stasis, and is found considerably more often in infertile men than in the general population, making it an important and treatable target during evaluation of the subfertile male partner.

Fill in the blank: Male factors contribute to roughly _____ of all infertility cases. _____ is the most common surgically correctable cause of male infertility.

5.2.2 Evaluation of male infertility

Evaluation begins with a detailed **history**, covering previous fertility, **sexual function**, exposure to **heat**, **toxins**, or **medications** affecting spermatogenesis, and relevant past illness such as **mumps** or **undescended testis**, alongside **examination** assessing **testicular size and consistency**, presence of a **varicocele**, and secondary sexual characteristics suggesting an underlying **hormonal disorder**.

Semen analysis remains the cornerstone investigation, assessing **sperm concentration**, **motility**, and **morphology** against World Health Organization reference values, with an abnormal result generally repeated after an interval given considerable natural variability, and further investigation, including **hormonal profile** and **genetic testing**, reserved for men with severely abnormal parameters or clinical features suggesting a specific underlying cause.

Fill in the blank: Semen analysis assesses sperm concentration, _____, and morphology. An abnormal semen analysis result is generally _____ after an interval given natural variability.

5.2.3 Management of male infertility

Management is directed at the identified cause: **surgical correction** for varicocele or obstruction, **hormonal treatment** for hypogonadotropic hypogonadism, treatment of any

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underlying **infection**, and **lifestyle modification** addressing modifiable factors such as **smoking**, **excessive alcohol**, **obesity**, and **occupational heat exposure**, all of which can measurably impair semen parameters.

Where a specific correctable cause cannot be identified or treatment is unsuccessful, **assisted reproductive techniques**, including **intrauterine insemination** for mild abnormalities and **in vitro fertilisation with intracytoplasmic sperm injection** for severe **oligospermia** or **azoospermia**, allow many men with otherwise untreatable infertility to father genetically related children.

Fill in the blank: Lifestyle factors that can impair semen parameters include smoking, alcohol, obesity, and occupational _____ exposure. Severe oligospermia may be managed with IVF and intracytoplasmic sperm _____.

Category
Pre-testicular Causes — **Endocrine disorders (hypogonadotropic hypogonadism), systemic illness, medications affecting hormone regulation**
Testicular Causes — **Genetic abnormalities (Klinefelter syndrome), mumps orchitis, testicular trauma, varicocele, radiation/chemotherapy damage**
Post-testicular Causes — **Obstructive azoospermia, congenital absence of vas deferens, infections (epididymitis), ejaculatory dysfunction**

Box 5.2: Categories of male infertility with example causes.

Pilot questions 5.2

1. Classify the causes of male infertility into pre-testicular, testicular, and post-testicular categories. (Linked to SLO 5.4)
2. Describe varicocele and its effect on male fertility. (Linked to SLO 5.4)
3. Describe the components of the history and examination in evaluating male infertility. (Linked to SLO 5.4)
4. Describe the parameters assessed on semen analysis and the reason an abnormal result is repeated. (Linked to SLO 5.4)
5. Discuss the management of male infertility, including lifestyle and assisted reproductive options. (Linked to SLO 5.5)

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Part 5.3: Investigation of the Infertile Couple

5.3.1 History and examination

Evaluation of the infertile couple begins with a **joint history** from both partners, covering **duration of infertility**, **coital frequency and timing**, **menstrual pattern**, previous **pregnancy history**, relevant **medical, surgical, and family history**, and specific enquiry about risk factors for **tubal disease**, such as previous **pelvic infection** or **abdominal surgery**, and for **ovulatory disorder**, such as **irregular cycles** or **hirsutism**.

Examination of the woman should assess **body mass index**, signs of **hyperandrogenism** such as **hirsutism** or **acne** suggesting polycystic ovarian syndrome, and pelvic examination for **uterine or adnexal abnormality**, while examination of the man should assess **secondary sexual characteristics**, **testicular volume**, and presence of a **varicocele**, with both partners' examinations contributing complementary information toward identifying the underlying cause.

Fill in the blank: History from the infertile couple should cover duration of infertility, coital frequency, and _____ pattern. Examination of the woman assesses BMI and signs of _____ suggesting PCOS.

5.3.2 Ovulation and tubal patency assessment

Ovulation is confirmed most reliably through a **mid-luteal serum progesterone** level, drawn approximately seven days before the expected next period, with a level above the reference threshold indicating ovulation has occurred, while **basal body temperature charting** and **urinary ovulation predictor kits** are less reliable but may still support the clinical picture in women with regular cycles.

Tubal patency is generally assessed through **hysterosalpingography**, a radiological study using contrast to outline the uterine cavity and fallopian tubes, or **laparoscopy with dye test**, which additionally allows direct visualisation of the pelvis for **endometriosis** or **adhesions**, with the choice guided by clinical suspicion, available resources, and whether other pelvic pathology needs to be assessed simultaneously.

Fill in the blank: Ovulation is confirmed most reliably through a _____ serum progesterone level. _____ additionally allows direct visualisation of the pelvis for endometriosis or adhesions.

5.3.3 Semen analysis and further investigations

Semen analysis should be performed as part of every couple's initial evaluation, regardless of which partner initially presents, since **male factor infertility** contributes to a substantial proportion of cases and evaluating both partners simultaneously avoids unnecessary delay in identifying the true underlying cause.

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Further investigation is guided by initial findings and may include **thyroid function tests** and **prolactin** where **ovulatory disorder** is suspected, **pelvic ultrasound** to assess **ovarian reserve** through **antral follicle count** and identify **fibroids** or **ovarian cysts**, and **anti-Müllerian hormone** measurement, a increasingly used marker of **ovarian reserve** that helps guide expectations and treatment planning, particularly in older women.

Fill in the blank: Semen analysis should be performed as part of every couple's _____ evaluation regardless of which partner presents first. _____ hormone is an increasingly used marker of ovarian reserve.

Investigation	Purpose
Ovulation Assessment	To confirm regular ovulation (e.g., mid-luteal progesterone, basal body temperature, ovulation kits)
Tubal Patency Testing	To evaluate fallopian tube openness and function (e.g., hysterosalpingography, sonohysterography, laparoscopy with dye test)
Semen Analysis	To assess sperm count, motility, and morphology
Hormonal Profile	To detect endocrine abnormalities affecting fertility (FSH, LH, prolactin, thyroid function tests)
Pelvic Ultrasound	To identify uterine or ovarian pathology (fibroids, polycystic ovaries, endometrial abnormalities)

Table 5.3: Key investigations in the infertile couple.

Pilot questions 5.3

1. Describe the key elements of history taken from an infertile couple. (Linked to SLO 5.6)
2. Describe the examination findings relevant to female and male infertility. (Linked to SLO 5.6)
3. Describe how ovulation is confirmed and the investigations used to assess tubal patency. (Linked to SLO 5.6)
4. Explain why semen analysis should be part of every couple's initial evaluation. (Linked to SLO 5.6)
5. Describe the further investigations used to assess ovarian reserve and other suspected causes. (Linked to SLO 5.6)

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Part 5.4: Assisted Reproductive Techniques

5.4.1 Ovulation induction and intrauterine insemination

Ovulation induction, using agents such as **clomiphene citrate**, **letrozole**, or **gonadotropins**, is the first-line treatment for women with **anovulatory infertility**, such as **polycystic ovarian syndrome**, stimulating follicular development and restoring regular ovulation in a substantial proportion of women, with treatment generally monitored using **ultrasound follicle tracking** to reduce the risk of **multiple pregnancy** from overstimulation.

Intrauterine insemination involves placing prepared **washed sperm** directly into the uterine cavity around the time of ovulation, bypassing the cervix, and is generally offered for **mild male factor infertility**, **unexplained infertility**, or where intercourse is difficult, often combined with **ovulation induction** to improve success rates, though it offers lower success per cycle than **in vitro fertilisation**.

Fill in the blank: Ovulation induction with clomiphene citrate is first-line treatment for _____ infertility such as PCOS. Intrauterine insemination involves placing prepared washed _____ directly into the uterine cavity.

5.4.2 In vitro fertilisation

In vitro fertilisation involves **controlled ovarian stimulation** with gonadotropins to develop multiple follicles, **oocyte retrieval** under ultrasound guidance, **fertilisation** of retrieved eggs with sperm in the laboratory, either conventionally or through **intracytoplasmic sperm injection** for severe male factor infertility, and **embryo transfer** of one or more resulting embryos into the uterine cavity several days later.

In vitro fertilisation is indicated for **tubal factor infertility**, **severe male factor infertility**, **endometriosis**, **unexplained infertility** after failed simpler treatment, and **advanced maternal age**, with success rates influenced strongly by **female age**, **ovarian reserve**, and **embryo quality**, and carrying recognised risks including **ovarian hyperstimulation syndrome** and an increased likelihood of **multiple pregnancy** where more than one embryo is transferred.

Fill in the blank: IVF involves controlled ovarian stimulation, oocyte retrieval, fertilisation, and embryo _____. Severe male factor infertility during IVF may require intracytoplasmic sperm _____.

5.4.3 Other techniques and ethical considerations

Additional techniques include **donor sperm** or **donor oocyte** use where a partner's own gametes are unusable, **surrogacy**, where another woman carries a pregnancy on behalf of the intended parents, and **fertility preservation** through **oocyte** or **embryo cryopreservation**, increasingly

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relevant for women delaying childbearing or facing treatment, such as **chemotherapy**, that threatens future fertility.

Ethical considerations surrounding assisted reproduction include the **cost and accessibility** of treatment, particularly relevant in resource-limited settings such as Nigeria where such services are rarely affordable or covered by insurance, the **disposition of unused embryos**, the use of **donor gametes** and questions of genetic parentage, and the **psychological and social implications** of treatments such as surrogacy, all of which require sensitive, individualised counselling rather than a one-size-fits-all approach.

Fill in the blank: Fertility preservation through oocyte or embryo _____ is increasingly relevant before treatments such as chemotherapy. A major ethical consideration is the cost and _____ of assisted reproduction, especially in resource-limited settings.

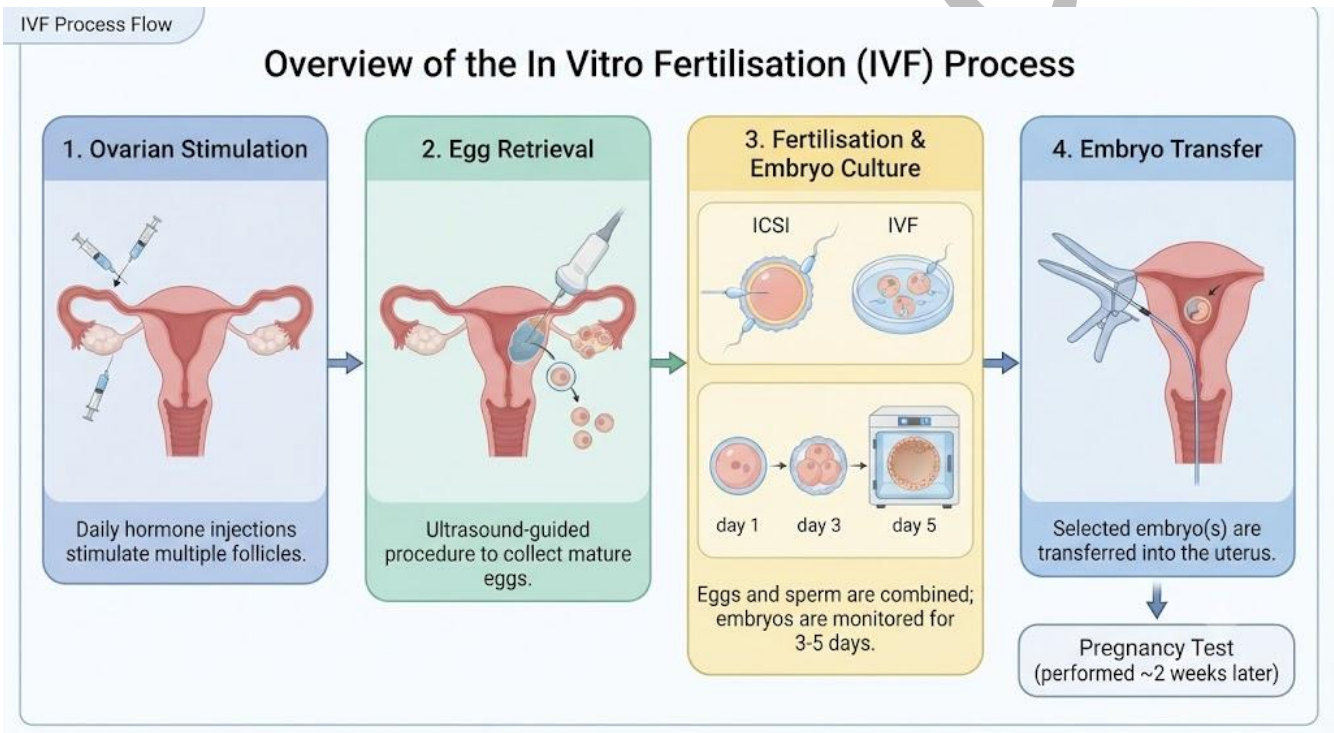

Figure 5.4: Overview of the in vitro fertilisation process.

Pilot questions 5.4

1. Describe the principles of ovulation induction and its main indication. (Linked to SLO 5.7)
2. Describe intrauterine insemination and its main indications. (Linked to SLO 5.7)
3. Describe the steps involved in in vitro fertilisation. (Linked to SLO 5.8)

4. Discuss the indications and risks associated with in vitro fertilisation. (Linked to SLO 5.8)
5. Discuss the ethical considerations relevant to assisted reproductive techniques, particularly in resource-limited settings. (Linked to SLO 5.8)

Series Summary

This Series examined **infertility**, beginning with its definition, classification into **primary** and **secondary infertility**, and its **epidemiology**, including the particular burden of secondary infertility linked to **pelvic infection** in Nigeria, alongside the principal causes of **female infertility**, from **ovulatory disorders** to **tubal**, **uterine**, and **unexplained** factors.

Male infertility was examined through its **pre-testicular**, **testicular**, and **post-testicular** causes, evaluation through history, examination, and **semen analysis**, and management options. The systematic investigation of the infertile couple was outlined, followed by the principal **assisted reproductive techniques**, including **ovulation induction**, **intrauterine insemination**, and **in vitro fertilisation**, alongside the important ethical considerations that accompany these treatments, particularly around cost, accessibility, and the use of donor gametes.

Glossary of Terms

- **Infertility:** the inability to conceive after twelve months of regular, unprotected intercourse.
- **Primary infertility:** infertility in a woman who has never previously conceived.
- **Secondary infertility:** infertility in a woman who has conceived previously, regardless of outcome.
- **Varicocele:** abnormal dilation of the veins draining the testis, the most common correctable cause of male infertility.
- **Oligospermia:** a reduced sperm concentration on semen analysis.
- **Azoospermia:** complete absence of sperm in the ejaculate.
- **Hysterosalpingography:** a radiological study using contrast to assess the uterine cavity and fallopian tube patency.
- **Anti-Müllerian hormone:** a hormone used as a marker of ovarian reserve.

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- **Ovulation induction:** pharmacological stimulation of ovulation, generally first-line treatment for anovulatory infertility.
- **Intrauterine insemination:** placement of prepared washed sperm directly into the uterine cavity.
- **In vitro fertilisation:** fertilisation of retrieved oocytes with sperm outside the body, followed by embryo transfer.
- **Ovarian hyperstimulation syndrome:** a recognised complication of controlled ovarian stimulation during fertility treatment.

Concept Check Questions [Series 5]

Objective questions

1. Infertility is defined as inability to conceive after _____ months of regular unprotected intercourse.
2. _____ infertility describes a woman who has never previously conceived.
3. _____ is the most common surgically correctable cause of male infertility.
4. Ovulation is confirmed most reliably through a mid-luteal serum _____ level.
5. _____ hormone is an increasingly used marker of ovarian reserve.

Short-answer questions

6. Describe the epidemiology of infertility and the particular burden of secondary infertility in Nigeria. (Linked to SLO 5.2)
7. Enumerate the principal causes of female infertility. (Linked to SLO 5.3)
8. Classify the causes of male infertility into pre-testicular, testicular, and post-testicular categories. (Linked to SLO 5.4)
9. Describe the key investigations used to assess ovulation and tubal patency. (Linked to SLO 5.6)
10. Describe the steps involved in in vitro fertilisation. (Linked to SLO 5.8)

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Long-answer questions

11. Define infertility, classify primary and secondary infertility, and describe its epidemiology. (Linked to SLO 5.1, SLO 5.2)
12. Enumerate the causes of female infertility and describe the causes and evaluation of male infertility. (Linked to SLO 5.3, SLO 5.4)
13. Describe the management of male infertility. (Linked to SLO 5.5)
14. Describe the systematic investigation of the infertile couple. (Linked to SLO 5.6)
15. Describe the principles of ovulation induction, intrauterine insemination, and in vitro fertilisation, including relevant ethical considerations. (Linked to SLO 5.7, SLO 5.8)

Answers to Concept Check Questions [Series 5]

Objective questions

1. Twelve.
2. Primary.
3. Varicocele.
4. Progesterone.
5. Anti-Müllerian.

Short-answer questions

6. One in six couples globally are affected; in Nigeria, secondary infertility is frequently linked to untreated pelvic infection following childbirth or unsafe abortion.
7. Ovulatory disorders, tubal factor infertility, uterine factors, endometriosis, cervical factors, and unexplained infertility.
8. Pre-testicular causes reduce gonadotropin stimulation; testicular causes include varicocele and genetic conditions; post-testicular causes include obstruction and ejaculatory dysfunction.
9. Mid-luteal serum progesterone confirms ovulation; hysterosalpingography or laparoscopy with dye test assess tubal patency.

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10. Controlled ovarian stimulation, oocyte retrieval, fertilisation in the laboratory, and embryo transfer into the uterine cavity.

Long-answer questions

11. **Basic response:** Infertility is inability to conceive after twelve months of regular unprotected intercourse, classified as primary or secondary, affecting roughly one in six couples globally with regional variation.

Value-added response: Secondary infertility in Nigeria is frequently linked to untreated pelvic infection, underscoring the importance of prompt treatment of postpartum and sexually transmitted infections.

12. **Basic response:** Female infertility arises from ovulatory, tubal, uterine, endometriosis-related, and unexplained causes, while male infertility arises from pre-testicular, testicular, and post-testicular causes evaluated with semen analysis.

Value-added response: Evaluating both partners simultaneously from the outset avoids unnecessary delay in identifying the true cause of a couple's infertility.

13. **Basic response:** Management of male infertility is directed at the identified cause, including surgical correction, hormonal treatment, and lifestyle modification, with assisted reproduction where needed.

Value-added response: Even severe male factor infertility can now be overcome through intracytoplasmic sperm injection, transforming outcomes for many previously untreatable men.

14. **Basic response:** Investigation includes joint history and examination, ovulation and tubal patency assessment, and semen analysis, guided further by suspected findings.

Value-added response: A systematic, couple-centred approach avoids the common but mistaken assumption that infertility investigation should begin with the woman alone.

15. **Basic response:** Ovulation induction and intrauterine insemination are first-line options for suitable causes, while in vitro fertilisation is used for more complex or resistant cases.

Value-added response: Ethical considerations, including cost, accessibility, and the use of donor gametes, require sensitive, individualised counselling, particularly in resource-limited settings.

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Answers to Pilot Questions [Series 5]

Part 5.1

6. Infertility is inability to conceive after twelve months; primary infertility describes a woman who has never conceived, secondary describes prior conception regardless of outcome.
7. The window for successful treatment narrows with declining ovarian reserve, so earlier evaluation allows timelier intervention.
8. About one in six couples globally are affected, with regional variation influenced by age, infection prevalence, and healthcare access.
9. Secondary infertility in Nigeria is frequently linked to untreated pelvic infection following childbirth or unsafe abortion, alongside considerable social stigma.
10. Ovulatory disorders, tubal factor infertility, uterine factors, endometriosis, cervical factors, and unexplained infertility.

Part 5.2

11. Pre-testicular causes reduce gonadotropin stimulation; testicular causes include varicocele, cryptorchidism, and genetic conditions; post-testicular causes include obstruction and ejaculatory dysfunction.
12. Varicocele is abnormal venous dilation impairing fertility through increased scrotal temperature, and is the most common surgically correctable cause.
13. History covers fertility, sexual function, exposures, and illness; examination assesses testicular size, varicocele, and secondary sexual characteristics.
14. Sperm concentration, motility, and morphology; repeated due to considerable natural variability between samples.
15. Surgical correction, hormonal treatment, lifestyle modification, and assisted reproduction including IUI or IVF with ICSI where needed.

Part 5.3

1. Duration of infertility, coital frequency and timing, menstrual pattern, pregnancy history, and risk factors for tubal disease or ovulatory disorder.
2. Female examination assesses BMI, hyperandrogenism, and pelvic findings; male examination assesses secondary sexual characteristics, testicular volume, and varicocele.

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3. Mid-luteal serum progesterone confirms ovulation; hysterosalpingography or laparoscopy with dye test assess tubal patency.
4. Male factor contributes to a substantial proportion of cases, so evaluating both partners together avoids delay in finding the true cause.
5. Thyroid function, prolactin, pelvic ultrasound for ovarian reserve and structural pathology, and anti-Müllerian hormone measurement.

Part 5.4

1. Pharmacological stimulation of ovulation with agents such as clomiphene citrate, first-line for anovulatory infertility such as PCOS.
2. Placement of prepared washed sperm into the uterine cavity, indicated for mild male factor or unexplained infertility.
3. Controlled ovarian stimulation, oocyte retrieval, fertilisation in the laboratory, and embryo transfer into the uterine cavity.
4. Indicated for tubal, severe male factor, endometriosis-related, and unexplained infertility; risks include ovarian hyperstimulation and multiple pregnancy.
5. Cost and accessibility, disposition of unused embryos, use of donor gametes, and psychological and social implications requiring sensitive counselling.

References and Attributions [Series 5]

1. Hoffman, B. L., Schorge, J. O., Halvorson, L. M. et al. (2020). Williams Gynecology (4th ed.). McGraw-Hill Education.
2. World Health Organization (2010). WHO Laboratory Manual for the Examination and Processing of Human Semen (5th ed.).
3. American Society for Reproductive Medicine (2021). Diagnostic Evaluation of the Infertile Female. Practice Committee Opinion.
4. Berek, J. S. and Berek, D. L. (2019). Berek and Novak's Gynecology (16th ed.). Wolters Kluwer.

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Figures, Plates, Tables, and Boxes

1. Figure 5.1: Principal causes of female infertility by category. AI-generated using the prompt: "Create a clean pie chart titled Principal Causes of Female Infertility by Category, showing proportional categories. Clinical educational diagram style."
2. Box 5.2: Categories of male infertility with example causes. AI-generated using the prompt: "Create a simple single-column reference box titled Categories of Male Infertility with Example Causes, organised by pre-testicular, testicular, and post-testicular level. Clean clinical reference box style."
3. Table 5.3: Key investigations in the infertile couple. AI-generated using the prompt: "Create a clean reference table titled Key Investigations in the Infertile Couple, listing investigation and purpose. Simple clinical reference table style with outside border."
4. Figure 5.4: Overview of the in vitro fertilisation process. AI-generated using the prompt: "Create a professional medical flowchart titled Overview of the In Vitro Fertilisation Process, showing stimulation, retrieval, fertilisation, and transfer stages. Clean clinical educational diagram style."

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