NEWS LINE

KARNATAKA ENDOCRINE SOCIETY

9th Issue | January 2026

Gynecological Endocrinology

PRESIDENT'S MESSAGE

Greetings from Karnataka Endocrine Society !

We wish all KES members and readers a very happy and prosperous New Year.

Welcome to the next edition of the KES Newsletter. Endocrinology encompasses disorders that involve several other specialties, Obstetrics and Gynecology, being one such important field. Reproductive endocrinology spans a wide spectrum, including pubertal disorders, menstrual abnormalities, fertility issues, and menopause. In most cases, close coordination between these two specialties is essential. There has been renewed interest in menopausal hormone replacement therapy in recent times. Keeping these aspects in mind, this edition of the newsletter has been curated.

I hope it will be of interest not only to obstetrician–gynecologists, but also to other specialists, including pediatricians and geriatricians.

I sincerely thank all my colleagues for their valuable contributions to this newsletter, and I extend my gratitude to the editors for dedicating their precious time and effort.

Your expert feedback is always welcome.

Thank you once again.

FROM THE EDITORS' DESK

We are pleased to present the 9th edition of the Karnataka Endocrine Newsletter. This issue focuses on Gynecological Endocrinology, an area of growing clinical relevance across all levels of healthcare.

Women's hormonal health presents unique challenges at different stages of life—from menstrual disorders in adolescence to pregnancy-related metabolic issues and menopause. This edition highlights commonly encountered clinical problems in gynecological practice, emphasizing their endocrine basis, long-term health implications, and the importance of timely intervention.

The articles offer practical, evidence-based guidance aimed at endocrinologists, gynecologists, and physicians, with a strong emphasis on multidisciplinary collaboration to improve women's health outcomes.

We sincerely thank all the contributors for their valuable expertise and commitment. We also appreciate the continued support of our readers. Your feedback and suggestions are welcome and will help guide future editions of the newsletter.

Warm Regards

Dr Rajeshwari
President
Karnataka Endocrine Society

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Honorary Secretary

Dr Aditi Chopra

Dr Vijay Sarathi

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DELAYED PUBERTY IN GIRLS: ENDOCRINE EVALUATION, RED FLAGS AND TREATMENT PATHWAYS

Delayed puberty in girls is a frequent referral to endocrine clinics, but only a subset have true pathology requiring intervention. A structured approach that distinguishes self-limited variants from hypogonadism, while not missing red flags, is central to good care.

Definition and epidemiology

Delayed puberty in girls is classically defined as absence of breast development (Tanner B2) by 13 years, or more than 5 years between thelarche and menarche, or absence of menarche by 16 years. Most adolescents have self-limited/constitutional delay, but approximately 15–20% harbor underlying chronic illness, primary ovarian failure, or central hypogonadism.

Clinical red flags which indicate significant pathology

These include poor growth velocity or height centiles drifting down on the growth chart; CNS symptoms, anosmia, headaches or visual changes; prior CNS irradiation or chemotherapy; history of cranial surgery, chronic systemic disease, or eating disorder; and stigmata of Turner syndrome or disorders of sex development (TS facies, webbed neck, cardiac anomalies, asymmetric or absent gonads)

Endocrine evaluation

Initial workup should integrate auxology, Tanner staging, and family pubertal history with targeted biochemistry and imaging. Baseline tests include serum LH, FSH, estradiol, TSH, free T4, prolactin, IGF-1, celiac screen (if indicated), and a left hand–wrist bone age; pelvic ultrasound helps assess uterine/ovarian size and identify gonadal streaks or agenesis. A High LH and FSH with low estradiol is a hypergonadotropicprofile-this mandates karyotype to exclude Turner syndrome and 46,XY DSD, while hypogonadotropic patterns require evaluation for chronic illness, undernutrition, pituitary hormone deficits and, when indicated, MRI sella.While hypergonadotropic pattern is easy to recognize,hypogonadotropic pattern can be confusing and may require a GnRH stimulation testing in select cases.

Distinguishing self-limited delay and hypogonadism

Self-limited delayed puberty typically shows delayed bone age, positive family history, preserved growth velocity, and spontaneous progression on follow-up. In contrast, congenital hypogonadotropic hypogonadism presents with persistently low sex steroids and inappropriately low/normal gonadotropins, absent spontaneous progression, and may be associated with cryptorchidism at birth, anosmia, or other pituitary deficits.

Treatment pathways

Management is individualized, balancing psychosocial distress, underlying etiology, and growth potential. While transdermal estradiol is preferred, it is not widely available in our country so predominantly estradiol valerate is used in clinical practice. In girls ≥13 years with self-limited delay and significant psychosocial impact, a short course of can be considered, at physiological starting doses of 0.5-1mg every other day with careful titration. In confirmed primary ovarian insufficiency or Turner syndrome, pubertal induction should mimic normal tempo over 2–3 years using low-dose oral estradiol valerate with later addition of cyclic progesterone once adequate breast development or breakthrough bleeding occurs, followed by lifelong hormone replacement for bone and metabolic health.

Long-term follow-up

Irrespective of etiology, adolescents require longitudinal follow-up for growth, bone accrual, metabolic health, and reproductive counseling. Attention to mental health, body image, and shared decision-making with the family is crucial to optimize adherence and transition to adult endocrine care.

DECODING THE CYCLE: ENDOCRINE CAUSES OF MENSTRUAL IRREGULARITIES


Dr. Aditi Rao Dr.Arpandev Bhattacharyya

The Normal menstrual cycle

The menstrual cycle is regulated through precise hormonal communication between the hypothalamus, pituitary, and ovaries. Pulsatile secretion of gonadotropin-releasing hormone (GnRH) stimulates the release of folliclestimulating hormone (FSH) and luteinizing hormone (LH), driving follicular development, ovulation, and subsequent progesterone production during the luteal phase. health. In the absence of implantation, progesterone levels fall, triggering a structured process of endometrial shedding. The stability of this axis ensures consistent cycle length, ovulatory function, and reproductive health.

When Hormones go wrong

Disruptions in the hypothalamic–pituitary–ovarian (HPO) axis can lead to abnormalities in ovulation, timing, bleeding patterns, or endometrial maturation. Common endocrine causes of menstrual dysfunction include polycystic ovary syndrome (PCOS), thyroid disorders, hyperprolactinemia, Cushing's syndrome, and primary ovarian insufficiency (POI). Pituitary disorders such as acromegaly and

non-functioning adenomas may impair gonadotropin signaling or prolactin regulation, contributing to irregular cycles. Weight-related conditions also play a role—hypothalamic amenorrhea in anorexia and hormonal dysregulation in morbid obesity can disrupt ovulation. Menstrual disturbances may precede other systemic signs, serving as an early and sensitive indicator of endocrine dysfunction.

Key mechanisms behind Endocrine Disorders

Polycystic Ovary Syndrome (PCOS)

PCOS involves insulin resistance, compensatory hyperinsulinemia, and ovarian theca-cell hyperandrogenism. Reduced sex hormone-binding globulin (SHBG) leads to elevated free androgens, impairing follicular development and disrupting the LH–FSH balance. Chronic anovulation results in oligomenorrhea or amenorrhea and contributes to endometrial instability. The interplay between metabolic and reproductive dysfunction explains its variable presentation.

Thyroid Disorders

Thyroid hormones influence GnRH secretion, gonadotropin levels, SHBG, and estrogen metabolism. Hypothyroidism can elevate TRH and prolactin, leading to anovulation and heavy, irregular cycles. Hyperthyroidism increases estrogen clearance, often causing shortened or infrequent periods. Both conditions compromise endometrial receptivity and disrupt cyclicity.

Hyperprolactinemia

Elevated prolactin suppresses GnRH pulsatility, reducing FSH and LH levels and leading to hypoestrogenism. This affects follicle development and luteal function. It often presents as oligomenorrhea or amenorrhea, sometimes with galactorrhea. Non-functioning pituitary adenomas may indirectly raise prolactin via stalk compression, producing similar effects.

Cushing's Syndrome

Excess cortisol suppresses GnRH and alters LH–FSH rhythmicity. Adrenal androgen overproduction and insulin resistance further impair ovulation. Menstrual cycles often become irregular or absent, reflecting cortisol's broad impact on reproductive regulation.

Premature Ovarian Failure / Primary Ovarian Insufficiency (POI)

POI involves early depletion or dysfunction of ovarian follicles, leading to low estrogen and elevated gonadotropins. Women often progress from oligomenorrhea to amenorrhea, with vasomotor symptoms or signs of estrogen deficiency. Causes include autoimmune oophoritis and FMR1 premutation. Early recognition is key for fertility, bone health, and cardiovascular protection.

Non-Classical Congenital Adrenal Hyperplasia (NCCAH)

NCCAH stems from partial 21-hydroxylase deficiency, resulting in elevated adrenal androgens and raised 17-hydroxyprogesterone. These impair olliculogenesis and ovulation, causing oligomenorrhea or secondary amenorrhea. It should be considered in hyperandrogenic women who do not meet full PCOS criteria.

Basics of Hormonal work-up for Menstrual Irregularity

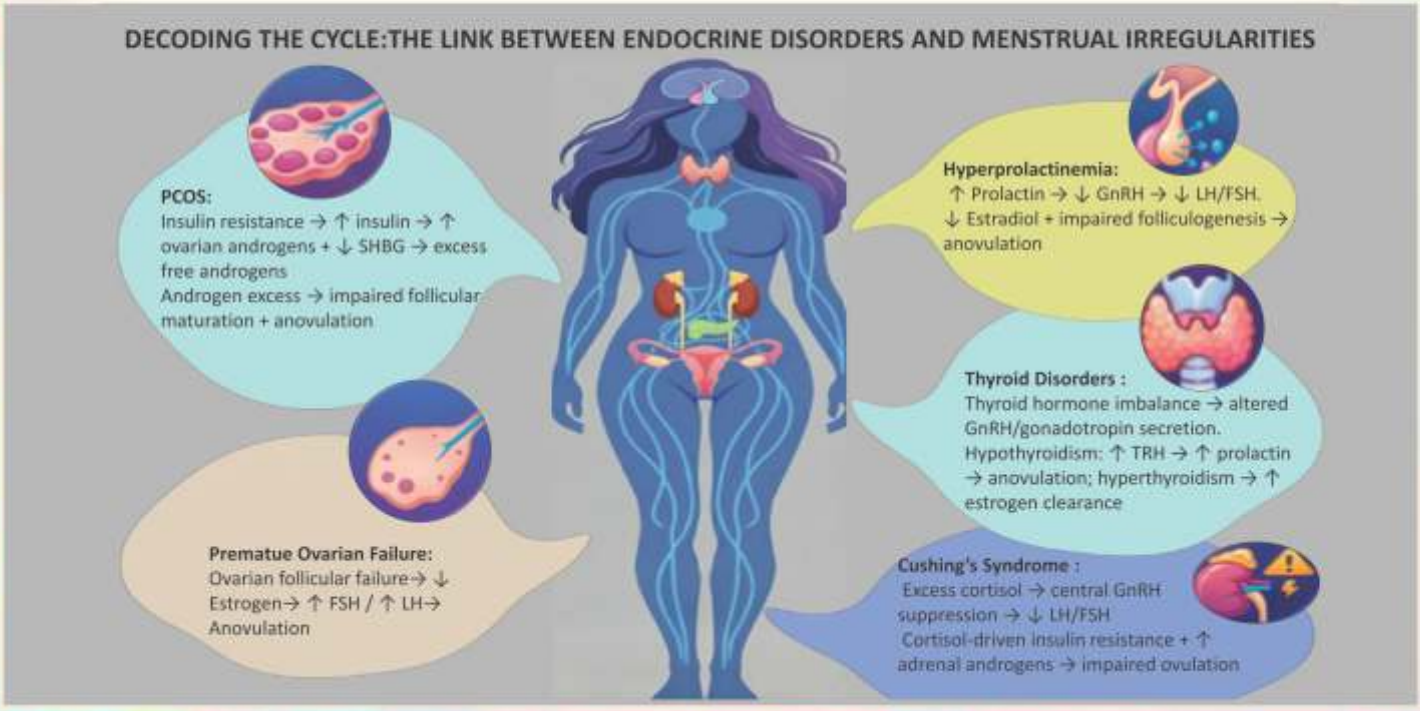
Evaluation begins with cycle documentation and exclusion of pregnancy. History should include weight changes, stress, thyroid symptoms, vasomotor features, galactorrhea, and signs of androgen excess. Obesity and anorexia nervosa both affect the HPO axis—via insulin resistance and peripheral estrogen in obesity, or GnRH suppression in anorexia. Physical exam includes BMI, acne or hirsutism, thyroid enlargement, and signs of estrogen deficiency or Cushingoid features. Key labs include TSH, free T4, prolactin, FSH, LH, and estradiol. These help differentiate pituitary, thyroid, ovarian, or hypothalamic causes. Total/free testosterone and DHEAS assess hyperandrogenic states like PCOS or NCCAH. 17-hydroxyprogesterone confirms NCCAH. HbA1c, glucose, or insulin identify metabolic contributors. Pelvic ultrasound evaluates ovarian morphology and endometrial thickness. MRI is reserved for suspected pituitary tumors or acromegaly based on clinical signs or lab abnormalities.

Treatment Guidelines

Management is tailored: lifestyle changes and oral contraceptives for PCOS; dopamine agonists for hyperprolactinemia; thyroid correction for dysfunction; and hormone replacement with fertility counselling for POI. In NCCAH, glucocorticoids may reduce androgens and improve cycles. Weight loss improves hormone balance in obesity; nutritional rehabilitation is critical in anorexia. Pituitary adenomas and acromegaly may require surgery or medication, often restoring cycles post-treatment.

Conclusion

Endocrine disorders are key contributors to menstrual irregularities in reproductive-age women. Conditions like PCOS, thyroid disease, hyperprolactinemia, Cushing's syndrome, POI, and NCCAH affect ovulation and endometrial function through distinct mechanisms. A targeted clinical and hormonal work-up enables early diagnosis and individualized care. Restoring hormonal balance is essential for improving cycle regularity, fertility, and long-term health.





Dr Shruthi Ravindra Dr Dhananjaya MS Dr Vijaya Sarathi

HIRSUTISM: A CASE BASED APPROACH

Case 1:

A 21-year-old woman presented with a three-year history of irregular menstrual cycles occurring every 45–60 days, which had gradually become more prolonged, along with progressive weight gain and facial acne. Family history was notable for type 2 diabetes in both parents.

On examination, her BMI was 28 kg/m^2 with mild acanthosis nigricans over the neck, and a modified Ferriman–Gallwey (mFG) score of 10 without virilization (clitoromegaly, deepening of voice) or Cushingoid features.

Laboratory evaluation revealed mildly elevated total testosterone (62 ng/dL), normal DHEAS (349 mcg/dL), normal prolactin (21 ng/mL), normal TSH (3.1 mU/L), and elevated LH (11.4 U/L) with normal FSH (4.1 U/L). Basal 17-hydroxyprogesterone was normal. Pelvic ultrasonography showed enlarged ovaries (right: 13 cc, left: 11 cc) with >20 peripherally arranged follicles and central echogenic stroma, consistent with polycystic ovarian morphology (PCOM). She was diagnosed with polycystic ovary syndrome (PCOS) and initiated on lifestyle modification and combined oral contraceptive pills.

Learning Points

1. Diagnosis of PCOS requires exclusion of thyroid dysfunction, hyperprolactinemia, adrenal disorders, and adrenal or ovarian tumors.
2. Although not diagnostic, a combination of high-normal to mildly elevated testosterone, features of insulin resistance and an increased LH: FSH ratio strongly suggests a diagnosis of PCOS.

Case 2:

A 16-year-old girl presented with gradually progressive facial hair, mild acne, and irregular menstrual cycles since early puberty. She reported pubarche at 6 years and menarche at 11 years.

Examination showed an mFG score of 12, normal BMI (21.2 kg/m2), blood pressure (110/70 mmHg), and normal secondary sexual characteristics (B5, P5) with a clitoral index of 30 mm^2. Laboratory evaluation revealed a total testosterone level of 86 ng/dL, with normal prolactin (20 ng/ml), TSH (2.3 mU/L), DHEAS (238 mcg/dL), and gonadotropins (FSH: 4.5 U/L, LH: 5.8 U/L). Pelvic ultrasound demonstrated 12-14 peripherally arranged small follicles suggestive of PCOM.

Basal 17-hydroxyprogesterone was mildly elevated (4.3 ng/mL), and ACTH-stimulated 17-OHP was 18.43 ng/mL, indicating non-classic congenital adrenal hyperplasia (21-hydroxylase deficiency).

She was treated with glucocorticoid replacement along with genetic counseling for CYP21A2 mutations. Follow-up showed significant clinical improvement and stable hormone levels.

Learning Points

PCOM may appear secondary to adrenal hyperandrogenism and does not exclude NCCAH.

In adolescents with slowly progressive hyperandrogenism, an elevated basal 17-OHP (> 2 ng/ml) followed by a marked ACTH-stimulated rise (10-100 ng/ml) strongly supports 21-hydroxylase–deficient NCCAH, helping differentiate it from PCOS.

Case 3:

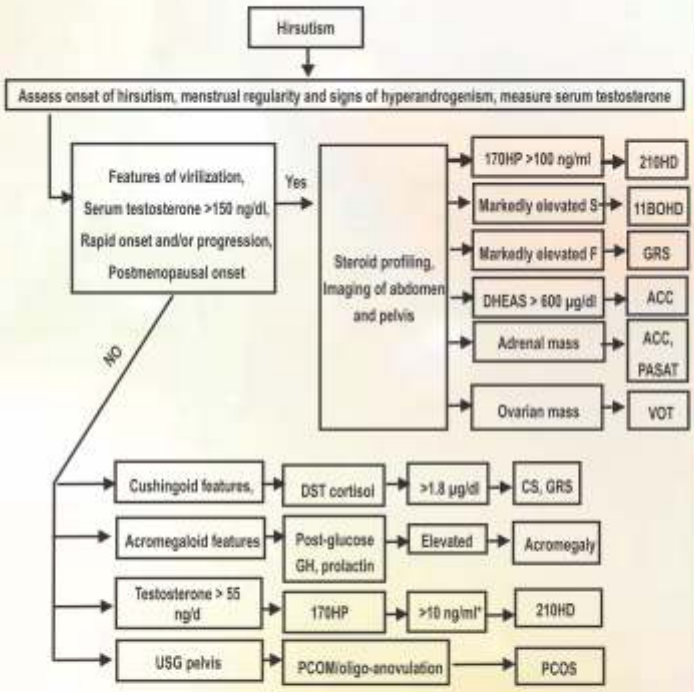
A 62-year-old postmenopausal woman presented with a six-month history of rapidly progressive coarse facial hair, acne, deepening of voice, and scalp hair loss. She had no symptoms suggestive of Cushing's syndrome.

Examination revealed marked hirsutism (mFG score: 24), cystic-nodular acne, androgenic alopecia, and clitoromegaly (clitoral index: 120 mm^2) without Cushingoid features.

Laboratory evaluation showed markedly elevated testosterone (359 ng/dL) with normal DHEAS (352 mcg/dL). Serum gonadotropins (FSH: 25 U/L, LH: 18 U/L) were low-normal range for postmenopausal state, and ONDST-cortisol was normal. Contrast-enhanced MRI of the abdomen and pelvis and transvaginal ultrasound did not identify a lesion in the ovary or adrenal glands. Serum testosterone was reduced to 30 ng/dl a week after intramuscular leuprolide (11.25 mg), indicating ovarian origin. Patient underwent bilateral oophorectomy, which revealed an 8 mm Leydig cell adenoma in the left ovary.

Learning Points

1. Rapid progression of hyperandrogenism in postmenopausal women strongly suggests an androgen-secreting tumor.
2. A combination of normal DHEAS, unsuppressed gonadotropins, and a decline in testosterone after GnRH agonist administration supports an ovarian, rather than adrenal, source of excess androgen.



*Corticotropin-stimulated. 11BOD: 11B-hydroxylase deficiency, 17OHP: 17-hydroxyprogesterone, 21OHD: 21-hydroxylase deficiency, ACC: adrenocortical carcinoma, CS: Cushing syndrome, DHEAS: dehydroepiandrosterone sulfate, DST: dexamethasone suppression test, F: cortisol, GH: growth hormone, GRS: glucocorticoid resistance syndrome, PASAT: pure androgen secreting adrenal tumor, PCOM: polycystic ovarian morphology, PCOS: polycystic ovarian syndrome, S: 11-deoxycortisol, US: ultrasonogram, VOT: virilizing ovarian tumor



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HYPERPROLACTINEMIA : WHEN TO SUSPECT, TEST AND TREAT

Introduction

Hyperprolactinemia is among the most frequently encountered endocrine abnormalities in routine practice and often presents diagnostic and therapeutic dilemmas. A structured, physiologybased approach allows clinicians to distinguish benign and reversible causes from pituitary pathology requiring longterm followup or intervention.

Physiology and Forms of Prolactin

Prolactin (PRL) is a 199aminoacid peptide hormone synthesized by lactotroph cells of the anterior pituitary. Its secretion is under tonic inhibitory control by hypothalamic dopamine, while thyrotropinreleasing hormone and estrogen act as stimulatory factors. Circulating prolactin exists in multiple molecular forms. Monomeric prolactin (≈23 kDa) is the most biologically active. Larger forms include dimeric prolactin ("big prolactin") and macroprolactin ("bigbig prolactin"), which is prolactin bound to immunoglobulin G. Macroprolactin has low bioactivity but may cause spuriously elevated serum prolactin levels, often in asymptomatic individuals.

When to Suspect Hyperprolactinemia

The following clinical presentations should alert to presence of possible hyperprolactinemia

Women (Premenopausal)

- Amenorrhea or oligomenorrhea
- Infertility and luteal phase defects
- Galactorrhea
- Decreased libido, vaginal dryness
- Long-term risk: osteopenia/osteoporosis due to hypogonadism

Men

- Decreased libido and erectile dysfunction
- Infertility, reduced sperm count
- Gynecomastia; galactorrhea (rare)
- Reduced muscle mass and bone density

Mass Effect (prolactinomas)

- Headache
- Visual field defects (classically bitemporal hemianopia)
- Cranial nerve palsies (rare)
- Hypopituitarism

Causes of Hyperprolactinemia

Table 1. Etiology of Hyperprolactinemia (Practical Classification)

Category	Examples	Typical Prolactin Levels	Key Clinical Clues
Physiological	Pregnancy, lactation, stress, sleep, exercise	Mild–moderate elevation	Context-specific, transient, asymptomatic
Drug-induced	Antipsychotics (risperidone, haloperidol), metoclopramide, antidepressants, opiates, methyldopa	Usually <100 ng/mL (may reach 200–250 ng/mL with metoclopramide/risperidone)	Temporal relation to drug initiation, reversibility on drug cessation
Pituitary – Prolactinoma	Microadenoma, macroadenoma	>250 ng/mL common; >500 ng/mL diagnostic of macroprolactinoma	Tumor size correlates with PRL, hypogonadism
Pituitary – Non-functioning adenoma	Stalk compression	Usually <100 ng/mL	Disproportionately low PRL for tumor size
Hypothalamic / stalk lesions	Craniopharyngioma, germinoma, infiltrative disorders	Mild–moderate elevation	Other pituitary hormone deficits
Systemic disorders	Primary hypothyroidism, CKD, cirrhosis, PCOS	Mild–moderate elevation	Improves with correction of underlying disease
Macroprolactinemia	PRL–IgG complexes	Variable, often mild–moderate	Minimal symptoms, PEG precipitation positive
Idiopathic	No identifiable cause	Mild elevation	May normalize spontaneously

Diagnosis: Key Principles

- **Single fasting serum prolactin** measurement is sufficient for diagnosis; avoid excessive venipuncture stress. Dynamic testing is **not required.**
- **Assay-specific reference ranges** must be used; upper limits are generally **< 25 ng/mL** in most laboratories.
- **Macroprolactin screening (PEG precipitation)** is essential in asymptomatic patients to prevent unnecessary imaging and treatment.
- **Serum prolactin correlates with tumor size:**
  - –> 250 µg/L strongly suggests a prolactinoma
  - –> 500 µg/L is virtually diagnostic of a macroprolactinoma
- **Mild–moderate elevations (< 100 ng/mL)** are commonly seen with **stalk compression** (non-functioning adenomas) or **drug-induced hyperprolactinemia.**
- Discrepancy between **large pituitary mass** and **modest prolactin elevation** should raise suspicion of assay interference.

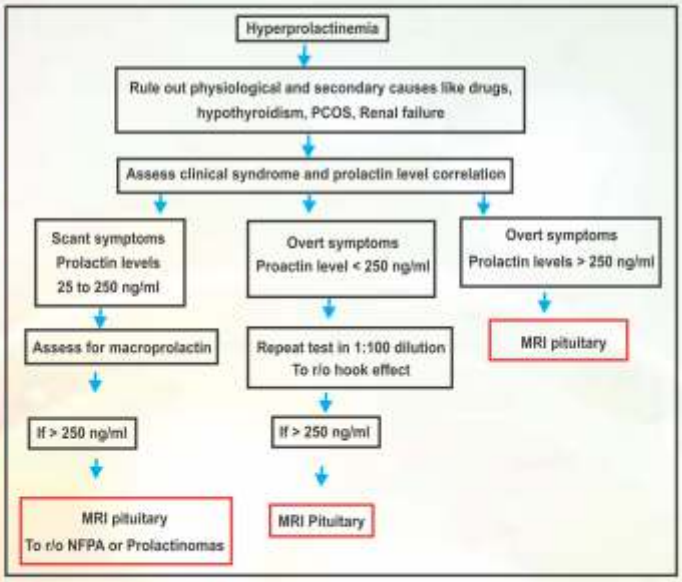
The Hook Effect – A Critical Pitfall

Occurs in patients with **very large prolactin-secreting tumors** where extremely high prolactin levels **saturate the assay,** leading to **falsely low measured values.**

Action point:

- Always **repeat prolactin after serial dilution** (typically **1:100**) when tumor size and prolactin levels do not correlate.

Stepwise approach to diagnosing hyperprolactinemia :



Management Strategies

Key principle: Management hinges on distinguishing patients who require active treatment from those who can be safely observed.

Drug-induced hyperprolactinemia:

- Asymptomatic cases do not require treatment.
- In symptomatic patients, withdrawal or substitution of the offending drug should be attempted, in consultation with the prescribing physician.

Prolactinomas – first-line therapy:

- Dopamine agonists are the treatment of choice for symptomatic prolactinomas.
- Cabergoline is preferred over bromocriptine due to higher efficacy, better tolerability, and greater tumor shrinkage.

Dosing:

- Cabergoline is typically used at 0.25–3 mg/week, titrated based on serum prolactin levels and clinical response.

Microprolactinomas:

- Asymptomatic patients generally require no treatment.
- Symptomatic patients benefit from dopamine agonist therapy.

Macroprolactinomas and refractory disease:

- Dopamine agonists remain first-line therapy.
- Resistance is defined as failure to normalize prolactin or achieve ≥50% tumor shrinkage on maximally tolerated doses.
- Transsphenoidal surgery is reserved for drug-intolerant or resistant cases, while radiotherapy is considered for aggressive or malignant tumors refractory to other treatments

Hyperprolactinemia and Pregnancy

Dopamine agonists should be discontinued once pregnancy is confirmed. Routine prolactin measurements and MRI are not indicated during pregnancy. Patients should be monitored clinically, with formal visual field assessment and MRI (without gadolinium) reserved for those who develop headaches or visual symptoms. Bromocriptine is the preferred agent if symptomatic tumor growth occurs during pregnancy.

Followup

After at least two years of successful dopamine agonist therapy with normalized prolactin levels and no visible tumor remnant, cautious dose tapering or discontinuation may be considered. Prolactin should be monitored every three months during the first year after withdrawal and annually thereafter, with repeat MRI if prolactin levels rise.

Biochemical Red Flags

- PRL >250 ng/mL → likely prolactinoma
- PRL >500 ng/mL → macroprolactinoma
- Large tumor + modest PRL → suspect hook effect (dilution needed)
- Asymptomatic elevation → evaluate for macroprolactin

Key Take-Home Messages

- **Measure smart, not more**

Single, well collected serum prolactin value confirmatory — dynamic testing unnecessary

Exclude before you image

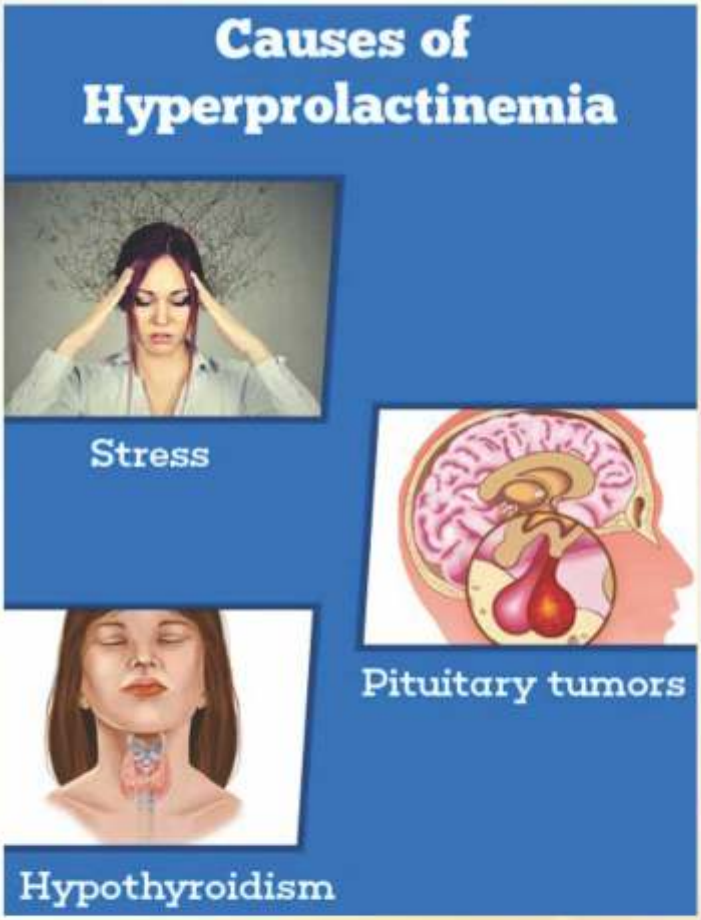
Pregnancy, drugs, hypothyroidism, renal disease, macroprolactin before ordering an MRI

- **Let numbers guide you**

Prolactin >250 ng/mL strongly suggests prolactinoma; >500 ng/mL is virtually diagnostic. A large tumor with modest prolactin mandates dilution to exclude the hook effect.

- **Treat selectively**

While cabergoline is first-line for symptomatic prolactinomas, many asymptomatic cases—especially drug-induced hyperprolactinemia—require observation alone



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POLYCYSTIC OVARY SYNDROME: BEYOND REPRODUCTIVE HEALTH

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting women of reproductive age, with a worldwide prevalence ranging from 4% to 21%. It is traditionally defined by ovulatory dysfunction (oligo/anovulation), hyperandrogenism (biochemical/ clinical) and polycystic ovarian morphology. However, this focuses only on the reproductive features of PCOS, and does not include the associated metabolic disturbances that are vital aspects of the clinical care bundle of PCOS. This review provides a brief overview of PCOS as a metabolic disease beyond a reproductive disease.

Metabolic disturbances in PCOS:

Dysglycaemia

Women with PCOS are about three times more likely to have Impaired glucose tolerance (IGT) and T2DM, and have an increased prevalence of IGT independent of BMI3. Another meta-analysis showed that the incidence of GDM among women with PCOS was similar between different BMI groups but higher in studies with a higher percentage of patients with overweight or obesity.

Obesity

The prevalence of obesity is significantly increased in women with PCOS compared with those without PCOS (risk ratio 2.77, 95% CI 1.88–4.10). Obesity exacerbates many aspects of the PCOS phenotype. Women with PCOS and obesity suffer from more severe hormonal, reproductive and metabolic derangements compared with their lean counterparts.

Dyslipidemia

Dyslipidemiais detected in almost 70% of affected women . PCOS is characterized by high triglycerides and low HDL cholesterol.

MASLD (Metabolic dysfunction-associated steatotic liver disease)

The reported prevalence of MASLD in women with PCOS is 15% to 55%. Elevated androgen levels and insulin resistance were observed as independent predictors of MASLD in PCOS.

Metabolic syndrome (MS)

Mscomprises centripetal obesity, hypertension, hyperglycemia and dyslipidemia. The odds of the MSwas more than threefold higher in women with PCOS than in control individuals. MS was more prevalent in the hyperandrogenicphenotype compared with the non-hyperandrogenic phenotype.

Cardiovascular disease

Women with PCOS have higher odds ratios for composite CVD (OR 1.68, 95% CI 1.26–2.23), composite ischaemic heart disease (OR 1.48, 95% CI 1.07–2.05), myocardial infarction (OR 2.5, 95% CI 1.43–4.38) and stroke (OR 1.71, 95% CI 2.20–2.44), and a higher incident rate ratio for cardiovascular mortality (OR 1.21, 95% CI 1.08–1.88) .

Cancer risk

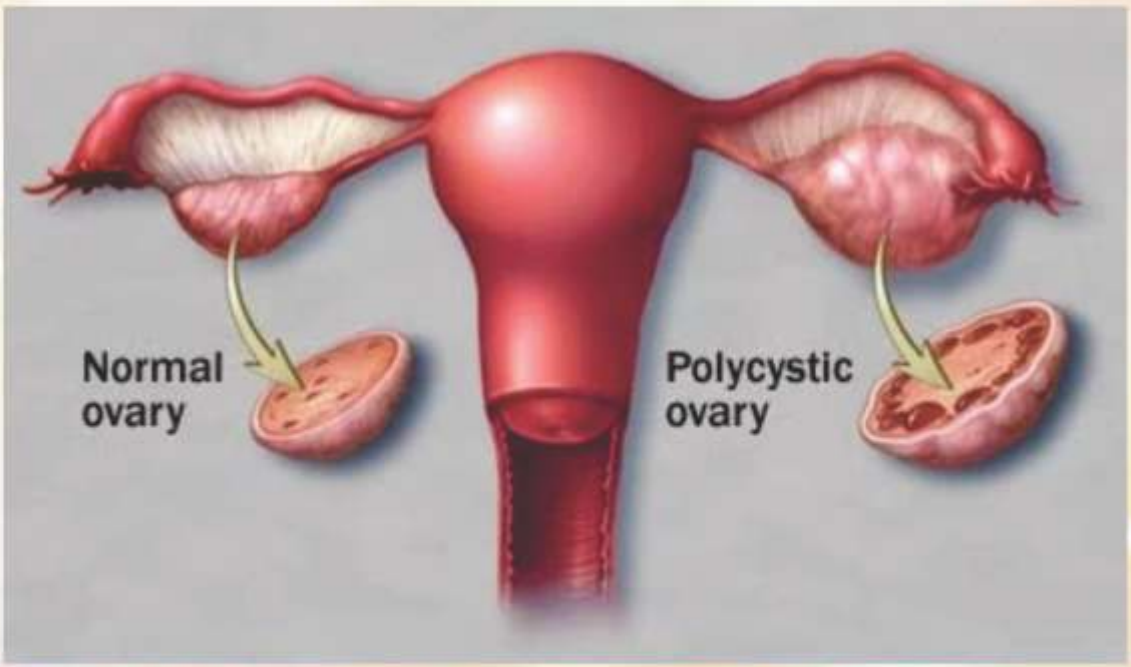
Women with PCOS have a three fold higher risk of developing endometrial carcinoma. The association between PCOS and Ovarian cancers is still unclear with some association with an increased risk of non-epithelial ovarian cancers. PCOS is also associated with a 1.9-fold higher risk of pancreatic cancer.

Mental Health

PCOS is associated with an increased risk of depression, anxiety, bipolar disorders and obsessive-compulsive disorder. The prevalence of anxiety and depressive disorders among women with PCOS ranges from 28% to 39% for anxiety and 11% to 25% for depression.

Conclusion:

PCOSis a heterogeneous disorder with reproductive and metabolic manifestations. The metabolic abnormalities of PCOS evolve across the lifespan and confer sustained cardio-metabolic risk, unlike the time-limited reproductive features. Patient education, early risk stratification & management of metabolic risk is key to comprehensive PCOS care.





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CLINICAL MANAGEMENT OF PREMATURE OVARIAN INSUFFICIENCY: FROM DIAGNOSIS TO LONG-TERM CARE

Premature Ovarian Insufficiency (POI) is a life-altering diagnosis affecting approximately 1% to 3.7% of women worldwide. Defined by the loss of normal ovarian activity before the age of 40, POI is clinically characterized by amenorrhea or oligomenorrhea with hypergonadotropic hypogonadism. Unlike natural menopause, POI is a pathological state associated with significant long-term health risks, including cardiovascular disease, osteoporosis, and neurocognitive decline, necessitating a proactive and comprehensive management strategy.

The causes can be classified as

- Genetic factors (e.g., Turner syndrome, Fragile X premutations)
- Autoimmune disorders
- Environmental factors (e.g., chemotherapy, radiation)
- Idiopathic (unknown causes)
- Surgical removal of ovaries

Diagnostic Criteria and Initial Workup The diagnosis of POI is confirmed when a woman under 40 presents with menstrual disturbance (amenorrhea or oligomenorrhea) for at least 4 months, accompanied by elevated Follicle-Stimulating Hormone (FSH) levels.

- **FSH Cutoff:** Serum FSH **>25 IU/L** on two separate occasions at least 4 weeks apart is the standard diagnostic criterion.
- **Estradiol:** Diagnosis typically involves low estradiol levels alongside elevated FSH.
- **AMH:** Anti-Müllerian Hormone (AMH) is a supportive marker for ovarian reserve; values ≤ **0.25 ng/ml** suggest POI with high sensitivity, though it is not a standalone diagnostic tool without FSH elevation.

Once diagnosed, the etiology must be investigated. While up to 90% of cases may be idiopathic, a karyotype is essential to rule out Turner syndrome (45,X) or mosaicism. Screening for the FMR1 premutation (Fragile X) is mandatory, as it accounts for a significant portion of familial cases. Furthermore, autoimmune screening for 21-hydroxylase antibodies (adrenal) and thyroid peroxidase antibodies is critical, given the frequent association with Addison's disease and hypothyroidism.

Therapeutic Management: Hormone Replacement Therapy (HRT) HRT is the cornerstone of POI management, distinct from postmenopausal therapy in that it replaces hormones the body should naturally be producing. Therapy should continue at least until the average age of natural menopause (50–51 years) to mitigate health risks.

Indications for HRT

- **Symptom Relief:** Treatment of vasomotor symptoms (hot flushes) and genitourinary atrophy.
- **Primary Prevention:** Critical for preventing bone mineral density loss and reducing cardiovascular morbidity.
- **Puberty Induction:** Required for adolescents presenting with primary amenorrhea to induce secondary sexual characteristics.

Contraindications for HRT

- **Absolute:** Current or personal history of hormone-sensitive cancers (e.g., breast cancer).
- **Relative/Cautionary:** History of venous thromboembolism (VTE) or thrombophilia requires hematological evaluation; in these cases, transdermal estradiol is preferred over oral formulations to avoid the hepatic first-pass effect and reduce thrombotic risk. Migraine and hypertension are not absolute contraindications but favor transdermal routes. (Image 1)

Drug Formulations and Doses Therapy aims to achieve physiological serum estradiol levels of approximately **100–150 pg/mL.**

- **Estrogen Replacement:** Transdermal Estradiol (Preferred):100 mcg/24h patch or 1.5–3 mg gel daily. This route bypasses the liver, offering a better safety profile regarding VTE and metabolic impact. Oral Estradiol:2–4 mg daily (estradiol valerate or micronized). Oral Conjugated Equine Estrogens: 0.625–1.25 mg daily, though natural estradiol is preferred.

- **Progesterone Replacement:** Mandatory for women with an intact uterus to prevent endometrial hyperplasia. Sequential Regimen (allows withdrawal bleed): Micronized progesterone 200 mg or Dydrogesterone10 mg for 12–14 days per month. Continuous Regimen: Micronized progesterone 100 mg or Dydrogesterone5 mg daily. Intrauterine Device: A Levonorgestrel-releasing IUD can provide endometrial protection and contraception.

Fertility and Psychological Support Patients must be counseled that POI is not synonymous with absolute sterility; intermittent ovarian function occurs, and spontaneous pregnancy rates are approximately 3–5%. For those actively seeking pregnancy, oocyte donation remains the most effective treatment, offering high cumulative pregnancy rates. Because the diagnosis can be psychologically devastating, causing anxiety and loss of self-esteem, a multidisciplinary approach involving psychological support is vital for long-term well-being. (Image 2)

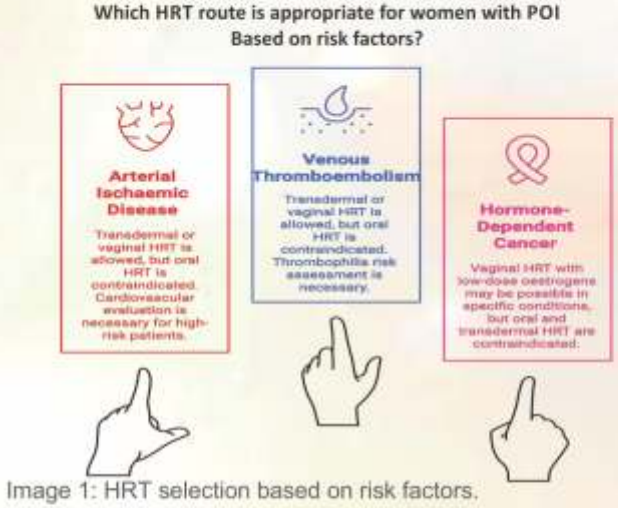

Image 1: HRT selection based on risk factors.

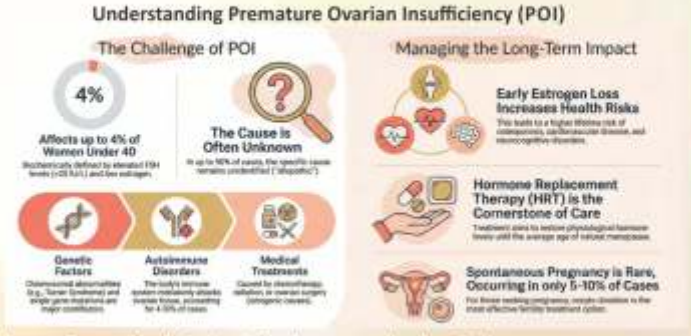

Image 2: graphical abstract of primary ovarian insufficiency.

GESTATIONAL DIABETES MELLITUS: DIAGNOSIS AND MANAGEMENT

Dr Sonali Appaiah

Dr Belinda George.

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disorder complicating pregnancy, with prevalence rising alongside increasing obesity and type 2 diabetes mellitus, particularly in South Asian populations. Hyperglycaemia detected during pregnancy is classified as either diabetes mellitus in pregnancy (DIP) or GDM(Figure1). DIP represents previously unrecognized type 1 or type 2 diabetes meeting diagnostic criteria for diabetes during pregnancy, while GDM refers to glucose intolerance first detected during pregnancy that does not meet criteria for overt diabetes. GDM is further subclassified into early GDM (diagnosed before 24 weeks) and standard GDM (diagnosed between 24–28 weeks).

Once regarded as a transient condition, GDM is now recognized to have important short- and long-term implications for both mother and offspring. It is associated with adverse pregnancy and perinatal outcomes, an increased risk of future type 2 diabetes and cardiometabolic disease in the mother, and a higher risk of obesity and metabolic disease in the offspring. Early detection and optimal management are therefore essential to improve outcomes across generations.

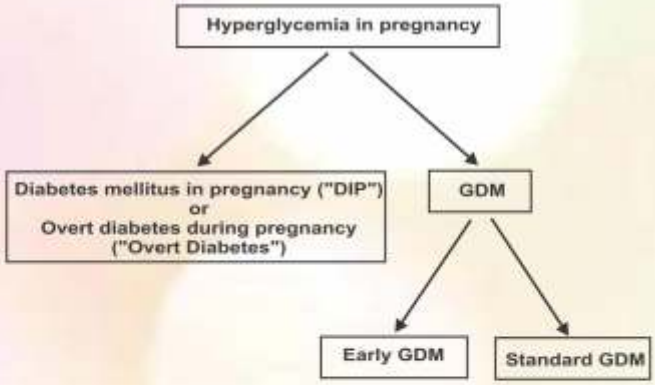

Figure 1. Classification of Hyperglycaemia in Pregnancy

Pathogenesis of Gestational Diabetes Mellitus

Pregnancy is characterized by progressive insulin resistance, particularly in the second and third trimesters, mediated by placental hormones such as human placental lactogen, placental growth hormone, and cortisol. In normal pregnancy, pancreatic β-cells compensate by increasing insulin secretion. GDM develops when this compensatory response is inadequate, reflecting limited β-cell reserve on a background of genetic susceptibility and metabolic risk factors.

Maternal hyperglycaemia results in increased placental glucose transfer, foetal hyperinsulinaemia, and accelerated foetal growth, explaining the association of GDM with macrosomia, large-for-gestational-age infants, and birth complications. Even mild degrees of hyperglycaemia are associated with adverse perinatal outcomes, underscoring the need for timely diagnosis and intervention.

Detection of Hyperglycaemia in Pregnancy

Screening for GDM is recommended at the first antenatal visit to detect previously undiagnosed diabetes, followed by repeat testing at 24–28 weeks of gestation, when insulin resistance peaks. High-risk women may require earlier or additional testing.

Universal screening is recommended in Indian population due to a high ethnic risk for GDM. The one-step 75-g oral glucose tolerance test (OGTT) with fasting, 1-hour, and 2-hour plasma glucose measurements is widely accepted. GDM is diagnosed if any value exceeds the recommended thresholds(Table 1). Alternative strategies, including two-step testing or single-sample testing, may be used in selected clinical or resource-limited settings. HbA1c is not recommended for diagnosing GDM due to physiological changes in pregnancy affecting its reliability. However, a HbA1c of ≥ 6.5% would suggest overt diabetes in pregnancy.

IADPSG Diagnostic Criteria for Hyperglycaemia in Pregnancy					
Gestational Diabetes Mellitus			Overt Diabetes in Pregnancy		
75 g OGTT	Fasting glucose	≥ 92mg/dl		Fasting glucose	≥ 126 mg/dl
	1hr PP glucose	≥ 180 mg/dl		2hr PP glucose/RBG	≥ 200 mg/dl
	2hr PP glucose	≥ 153 mg/dl			

Table 1. IADPSG Diagnostic Criteria for Hyperglycaemia Detected During Pregnancy.(IADPSG- International Association of Diabetes and Pregnancy Study Groups, OGTT-75-g oral glucose tolerance test, PP-Postprandial, RBG-Random Plasma Glucose.)

Management of Hyperglycaemia in Pregnancy

The primary goals of GDM management are to maintain near-normal glycaemia, prevent excessive foetal growth, and minimize maternal and neonatal complications. Management is individualized and includes lifestyle modification, glucose monitoring, and pharmacotherapy when required.

Lifestyle Modification

Medical nutrition therapy is the cornerstone of GDM management. Diet should provide adequate calories and carbohydrates to support foetal growth while minimizing postprandial hyperglycaemia. Emphasis should be placed on low glycaemic index carbohydrates, adequate protein, dietary fibre, and healthy fats. Excessive carbohydrate restriction and ketosis should be avoided.

Regular physical activity, such as moderate-intensity walking for at least 30 minutes daily, improves insulin sensitivity and postprandial glucose levels, provided there are no obstetric contraindications. Lifestyle measures alone might be sufficient in approximately 70–85% of women with GDM.

Monitoring and Targets

Self-monitoring of blood glucose (SMBG) is essential for assessing glycaemic control and guiding therapy. Monitoring typically includes fasting and postprandial measurements, with frequency individualized according to treatment intensity.

Glycaemic targets during pregnancy are lower than in the non-pregnant state to reduce the risk of foetal hyperinsulinemia and overgrowth (Table 2). HbA1c may be used as a secondary measure of glycaemic control but does not replace SMBG. Continuous glucose monitoring (CGM) is particularly useful in women with type 1 diabetes, high glycaemic variability, or recurrent hypoglycaemia and helps optimize time-in-range during pregnancy.

Glucose Measurement	Glycaemic targets in Pregnancy
Fasting glucose	< 95
1hr PP glucose	< 140
2hr PP glucose	<120

Table 2. Glycaemic targets in pregnancy as per ADA recommendation. (ADA- American Diabetes Association, PP- Postprandial)

Pharmacological Therapy

Pharmacotherapy is initiated when lifestyle measures fail to achieve glycaemic targets within 1–2 weeks or when hyperglycaemia is significant at diagnosis. Insulin remains the gold standard therapy, as it does not cross the placenta and allows precise dose titration. Basal–bolus regimens using modern insulin analogues are preferred due to better physiological profiles and a lower risk of hypoglycaemia.Insulin requirements may decrease in early pregnancy and rise progressively during the second and third trimesters, necessitating frequent dose adjustments.

Metformin is increasingly used in women with GDM and is effective in improving glycaemic control with less maternal weight gain and lower neonatal hypoglycaemia. However, it crosses the placenta and has been associated with a slightly higher risk of small-for-gestational-age infants and preterm birth in some studies, with limited long-term offspring data. Therefore, its use requires careful patient counselling.Sulfonylureas are generally avoided.

Peripartum and Postpartum Care

The timing and mode of delivery should be individualized based on glycaemic control, foetal growth, and obstetric considerations. During labour, maternal glucose levels should be closely monitored to reduce neonatal hypoglycaemia. Following delivery, insulin resistance declines rapidly; most women with GDM achieve normoglycaemia without pharmacotherapy, while women with overt diabetes require prompt reduction and adjustment of insulin doses.

Women with GDM should undergo a 75 g OGTT 4–12 weeks postpartum to detect persistent dysglycaemia. Long-term follow-up is essential, as up to 50% may develop type 2 diabetes within a decade. Offspring are also at increased risk of obesity and metabolic disease, highlighting the importance of breastfeeding, healthy lifestyle practices, and ongoing surveillance.

Conclusion

GDM represents a critical opportunity for early intervention to improve immediate pregnancy outcomes and long-term metabolic health. Universal screening in high-risk populations, timely diagnosis, meticulous glycaemic control, and structured postpartum follow-up are essential. A multidisciplinary approach involving physicians/endocrinologists, obstetricians, and diabetes educators is key to breaking the intergenerational cycle of diabetes.

MENOPAUSE & HORMONE REPLACEMENT THERAPY (HRT)

Dr Ganavi Y.P

Dr Pramila Kalra

Menopause represents a critical biological and clinical transition in a woman's life, marked by estrogen deficiency and associated systemic consequences affecting quality of life, musculoskeletal health, and long-term cardiometabolic risk. The STRAW+10 system provides a standardized framework for staging reproductive aging. It helps us differentiate perimenopause, early postmenopause, and late postmenopause, which is critical because timing of hormone therapy initiation strongly influences outcomes. Early menopause is defined as menopause occurring between 40–45 years, while primary ovarian insufficiency(POI) occurs before 40 years. These women have prolonged estrogen deficiency and represent a unique high-risk group requiring proactive hormone replacement.

Menopause Hormonal Therapy(MHT) is FDA-approved for:

- Moderate to severe vasomotor symptoms: Therapy can be initiated even in late perimenopause if symptoms are severe.
- Moderate to severe genitourinary syndrome of menopause: Vaginal Estrogen therapy (ET) is used, low dose can be initiated even beyond 60 years and continued for extended duration, if needed even in women where systemic therapy is contraindicated, with oncology consultation when required.
- Prevention of osteoporosis: MHT reduces fracture risk when initiated early but is not recommended solely for osteoporosis treatment in women over 60.
- Premature hypoestrogenism such as early menopause, POI, or bilateral oophorectomybefore 45 years: should receive MHT until the average age of natural menopause not only to reduce symptoms of hypoestrogenism but also to reduce cardiovascular and osteoporosis risk and to prevent cognitive impairment.Hormone replacement—not oral contraceptives—is preferred to achieve physiological estradiol levels and provide long-term protection.

According to American Heart Association(AHA) and North American Menopause Society(NAMS), MHT may reduce cardiovascular risk only when initiated within 10 years of menopause or before age 60 as initiation of MHT early and continuation while endothelium is intact, maintains vascular health, and reducesvascular aging and progression of atherosclerosis. It is not recommended for primary prevention of cardiovascular disease when started late as estrogen increases inflammatory mediators and causes plaque instability. Ideal candidates are women <60 years, menopause duration <10 years, with favourable lipid profiles and absence of metabolic syndrome or venous thromboembolism risk. Proper selection is key to safety.It is imperative to calculate each patient's risk for Atherosclerotic cardiovascular disease(ASCVD) by ASCVD risk calculators prior to initiating MHT. MHT is not recommended solely for dementia prevention. However, early use may improve mood and depressive symptoms.

Types of MHT:

Women with an intact uterus require estrogen plus progestogen (EPT) or a tissue-selective estrogen complex (TSEC). Women post-hysterectomy can receive estrogenalone.Other options include tibolone and ospemifene depending on indication.

The goal is to use the lowest effective dose to achieve symptom relief. Estrogen alone treats symptoms, while progesterone is added for endometrial protection in women with a uterus. Different routes of systemic oestrogen preparations include oral, transdermal, vaginal ring. Amongst oral, 17 beta oestradiol, oestradiol valerate and conjugated equine estrogenare available. Among transdermal, estradiol gel, patch and spray are available. Transdermal estrogen is preferred over oral due to better cardiovascular and metabolic safety. Among oral agents, lower doses are always preferred over higher doses. Both oral and transdermal estrogen are acceptable options for vasomotor symptoms. However, in women with hypertension, diabetes, hypertriglyceridaemia, obesity / metabolic syndrome, transdermal estrogen is preferred over oral estrogen. This is because transdermal estrogen:

- Avoids first-pass hepatic metabolism
- Has minimal effect on coagulation factors
- Does not significantly increase triglycerides
- Has less impact on inflammatory markers such as CRP

Thus oral estrogen should be avoided or used with caution or transdermal route is preferred in women with:

- Venous thromboembolism(VTE) risk or family history of VTE
- Poor symptom control with oral therapy
- Gastrointestinal absorption issues
- Migraine, especially with aura
- Obesity, smoking, sedentary lifestyle
- Stroke risk factors
- Gallstone disease or cholecystitis
- Hypertension, diabetes, hypertriglyceridaemia, obesity / metabolic syndrome

If transdermal estrogen is unavailable or unacceptable, 17 beta estradiol is preferred over valerate which is preferred over conjugated equine estrogen (CEE) and lowest effective dose is recommended. This is because estradiol has less stimulation of hepatic ER-beta receptors, less induction of inflammatory mediators and more physiological estrogen profile compared to CEE.

The different types of progesterone therapies include progesterone derivatives(dydrogesterone, medroxyprogesterone acetate), testosterone derivatives(levonogestrel, norgestrel), drosperinone or micronized progesterone and combined therapies are also available.Micronized progesterone is preferred due to its neutral effects on breast cancer risk, metabolic, cognitive and vascular profile as compared to medroxyprogesterone acetate.

Progesterone preparations

ORAL PROGESTIN TABLET	
Medroxyprogesterone acetate	2.5, 5, 10 mg/day
Norethindrone	0.35 mg/day
Dydrogesterone	10mg/day
Drospirenone	4mg
ORAL PROGESTERONE CAPSULE	
Micronized progesterone	100, 200 mg/day

Systemic estrogenpreparations

ORAL ESTROGEN TABLETS	
Micronized E2	0.5, 1, 2 mg/day
Estradiol valerate	1.5 g/day
CEE	0.3, 0.45, 0.625 mg/day
TRANSDERMAL ESTROGENS	
Estradiol patch	0.025 to 0.1 mg once or twice weekly
Estradiol percutaneous gel	0.25 – 1.5mg qd
Estradiol transdermal spray	1.5 mg qd

The different regimes of MHT are cyclical and continuous combined regime. Progesterone preparation is added to the existing estrogen preparation in last 14 days in cyclical regime and this is preferred in perimenopausal women. The regime used in postmenopausal women is continuous where progesterone is continuously continued with estrogen.

Tibolone has estrogenic, progestogenic, and androgenic effects. It improves vasomotor symptoms, mood, and libido but should only be used after 12 months of menopause. It is contraindicated in breast cancer survivors. Ospemifene is a selective estrogen receptor modulator used for dyspareunia. It may worsen vasomotor symptoms and increases venous thromboembolism and endometrial hyperplasia risk, so patient selection is crucial. TSECs combine estrogen with a SERM, providing endometrial protection without progesterone. They are useful in women intolerant to progestogens.

Discontinuation of MHT:

There is no clear recommendation on abrupt versus tapering discontinuation. Approximately 50% of women experience recurrence of symptoms after stopping MHT. Initiate alternative nonhormone interventionsor periodic trials of lowering or discontinuing hormone therapycan be tried. Promptly re-evaluate and discontinue if:

- Any new contraindication (such as a VTE, stroke, or hormone-sensitive cancer)
- Significant change in health status or lifestyle

Using MHT with caution:

MHT can be considered for short duration and with lowest effective doses in women with:

- Family history of breast cancer alone
- Prior benign breast biopsy
- Women who have undergone prophylactic oophorectomy for BRCA1 or BRCA2 variants, where hormone replacement is often appropriate
- Gall bladder disease
- Hypertriglyceridemia
- Diabetes
- Migraine with aura
- Risk of ASCVD

Contraindications:

Absolute contraindications include undiagnosed abnormal genital bleeding, known/suspected or history of breast cancer/estrogen dependent cancer like endometrial cancer,history or active DVT/ pulmonary embolism, active/history of arterial thromboembolic disease (stroke, MI), and history/active liver disease, known Protein C, Protein S or antithrombin deficiency. Non-hormonal options should be explored in these cases.

Menopausal hormone therapy is underutilized due to outdated fears. When prescribed early, appropriately, and individually, it is safe and effective for symptom control and long-term health.Always assess age, time since menopause, route of delivery, and individual risk factors such as ASCVD, VTE, breast cancer, and liver disease before prescribing.

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