AOGD BULLETIN

Volume 19 I January 2020 I Monthly Issue 9 I Price ₹30 Only

Enlightening the Path for Next Generation of Gynaecologists

Dedicated Issue:
Gynae Endocrinology

AOGD SECRETARIAT
Department of Obstetrics & Gynaecology,
3076, Teaching Block, IIIrd Floor, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029
Tel.: 011-26546603, 26593221 E-mail: secretaryaogd2019@gmail.com
Website: www.aogd.org

AOGD Bulletin

Volume 19 • Monthly Issue 9 • January 2020

AOGD Secretariat
Department of Obstetrics and Gynecology
3076, Teaching Block, IIIrd Floor
All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029
Tel No: 011-26546603, 26593221
Email: secretaryaogd2019@gmail.com
www.aogd.org

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  Anju Singh

Publisher/Printer/Editor
Dr J B Sharma on behalf of Association of Obstetricians & Gynecologists of Delhi.

Printed at
Process & Spot C-112/3, Naraina Industrial Area, Phase-1, New Delhi 110 028

Published from
Department of Obstetrics and Gynecology
All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029

Editor
Dr J B Sharma
Ph. No. 011-26546603; Email: secretaryaogd2019@gmail.com

Total number of pages = 52

From the President's Pen

Happy New Year – 2020

Friends current issue of AOGD Monthly bulletin is devoted to subspecialty of Gynaecological Endocrine Disorders. In fact our specialty deals with various aspects of Endocrine conditions more than any other branch of medicine.

We have seen a changing pattern in endocrine conditions. PCOS, hirsutism have taken over the earlier conditions of Amenorrhea etc. A sound knowledge of these conditions which we see in day to day practice will go a long way round in helping management of patients in a scientific way.

Happy Reading

Dr Sunesh Kumar
President, AOGD

From the Secretary's Desk

Dear Friends,

Warm wishes for a very happy, healthy and prosperous 2020, from the AOGD Secretariat at AIIMS. The December issue on "Medical Disorders in Pregnancy" has been appreciated and I want to thank you all for it.

The subject of gynecologic endocrinology is always challenging and tricky. So, here we bring out our latest bulletin hoping it will enable a better comprehension of topic and help in managing patients in day to day practice. Hope you all find it interesting and useful

The activities in the month of December included, a Quality Improvement Workshop at AIIMS on 14th under the aegis of Quality Improvement subcommittee of AOGD. On 17th a CME was organized by FOGsD with FOGSI and AOGD and the monthly meeting was held at Sir Ganga Ram Hospital.

We look forward to your continued support.

Warm regards

Dr Vatsla Dadhwal
Hon. Secretary

Monthly Clinical Meeting

Monthly Clinical Meet will be held at Dr RML Hospital, New Delhi
on **Friday, 17th January, 2020 from 04:00pm to 05:00pm**.

From the Editor's Desk

Dr J B Sharma
Editor

Dr Garima Kachhawa
Guest Editor

Dr Reeta Mahey

Dr P Vanamail

Dr Vidushi Kulshreshtha

Co-Editors

We are delighted to write the Editorial for this month's bulletin on the special issue on Gynae Endocrinology which is an important emerging specialty of Gynaecology. We have interesting and clinically useful article on "Evaluation of Amenorrhea" by Dr Shruthi Bhaskaran and Dr Abha Sharma from UCMS & GTB hospital which will be very useful to the esteemed readers in their day to day practice.

Polycystic Ovaries Syndrome is becoming rampant all over the world. It has taken epidemic proportion and is associated with short and long term adverse outcomes including metabolic syndrome apart from menstrual dysfunction and infertility.

We have clinically useful article on "Adolescent polycystic Ovary Syndrome – Still an Enigma" by Dr Megha Mittal and Dr Pratima Mittal from VMMC & Safdarjung Hospital and "Long term consequences of PCOS" by Dr Pikee Saxena from LHMC. We have another important article on "Hirsutism" by Dr. Kusumlata and Dr. Alka Kriplani which will be very useful for the clinicians.

Another important and difficult topic "XY Female" has been made simple by Dr Deepti Goswami & Dr Mrinalini Dhakate from MAMC Delhi. Dr Rakhi Malhotra & Dr Rajesh Khadgawat from Endocrinology department of AIIMS have written an interesting article on "Turner Syndrome" including guidance for hormonal therapy.

"Pre-menstrual Syndrome" is an agonising condition for the sufferers. Dr. Mala Srivastava from Sir Ganga Ram Hospital enlightens us about its diagnosis and management. Dr Sonali Jain, Dr Radhika from UCMS & GTB Hospital enlighten us about "Recent update on postmenopausal Hormonal therapy" which would be very useful for the readers in their practice. Dr Tarang Preet and Dr. Vidushi Kulshrestha have covered "Hyperprolactinaemia" for better understanding of this condition causing menstrual dysfunction, galactorrhea and infertility.

We have an interesting journal scan on useful articles by Dr Archana Minz, Dr Juhi Bharti, Dr. Rinchen and Dr. Shainy which will be useful for our readers.

We wish our esteemed readers a happy reading and shall welcome their comments.

Editorial Team

Evaluation of Amenorrhea

Sruthi Bhaskaran[1], Abha Sharma[2]
[1]Associate Professor, [2]Senior Specialist & Medical Superintendent (MCH), Department of Obstetrics & Gynecolgy UCMS/GTB Hospital, New Delhi

When approached logically and systematically, the diagnostic evaluation of amenorrhea truly is straightforward, involving thorough history taking and a finite number of laboratory tests and procedures already familiar to almost all clinicians.

The purpose of this chapter is to provide a systematic strategy for the evaluation of amenorrhea that will yield an accurate diagnosis.

Definition of Amenorrhea[1]

- No menses by age 13 in the absence of growth or development of secondary sexual characteristics
- No menses by age 15 regardless of the presence of normal growth and development of secondary sexual characteristics
- In women who have menstruated previously, no menses for an interval of time equivalent to a total of at least three previous cycles or no menses over a 3-month period.

  It is important to point out that unduly strict adherence to these criteria with a disregard to the overall clinical picture can result in a delay in identifying serious underlying health conditions. For example, there is no reason to defer the evaluation of a young girl who presents with the classical phenotype of Turner syndrome. Similarly, a 14-year-old girl who has no vagina should not be advised to return in 2 years before initiating evaluation and offering intervention. All patients deserve a considerate evaluation at initial presentation.[2] Finally, the possibility of pregnancy as a reason for amenorrhea must always be considered.

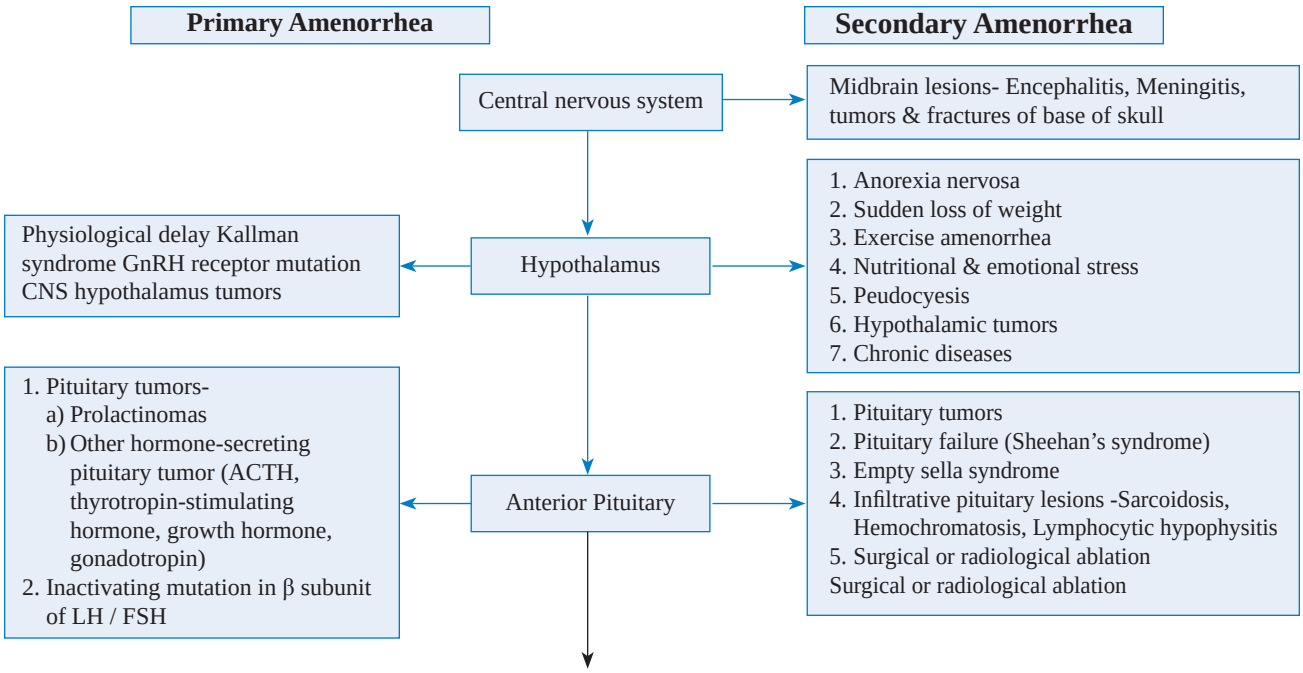
Traditionally, amenorrhea has been categorized as primary or secondary.

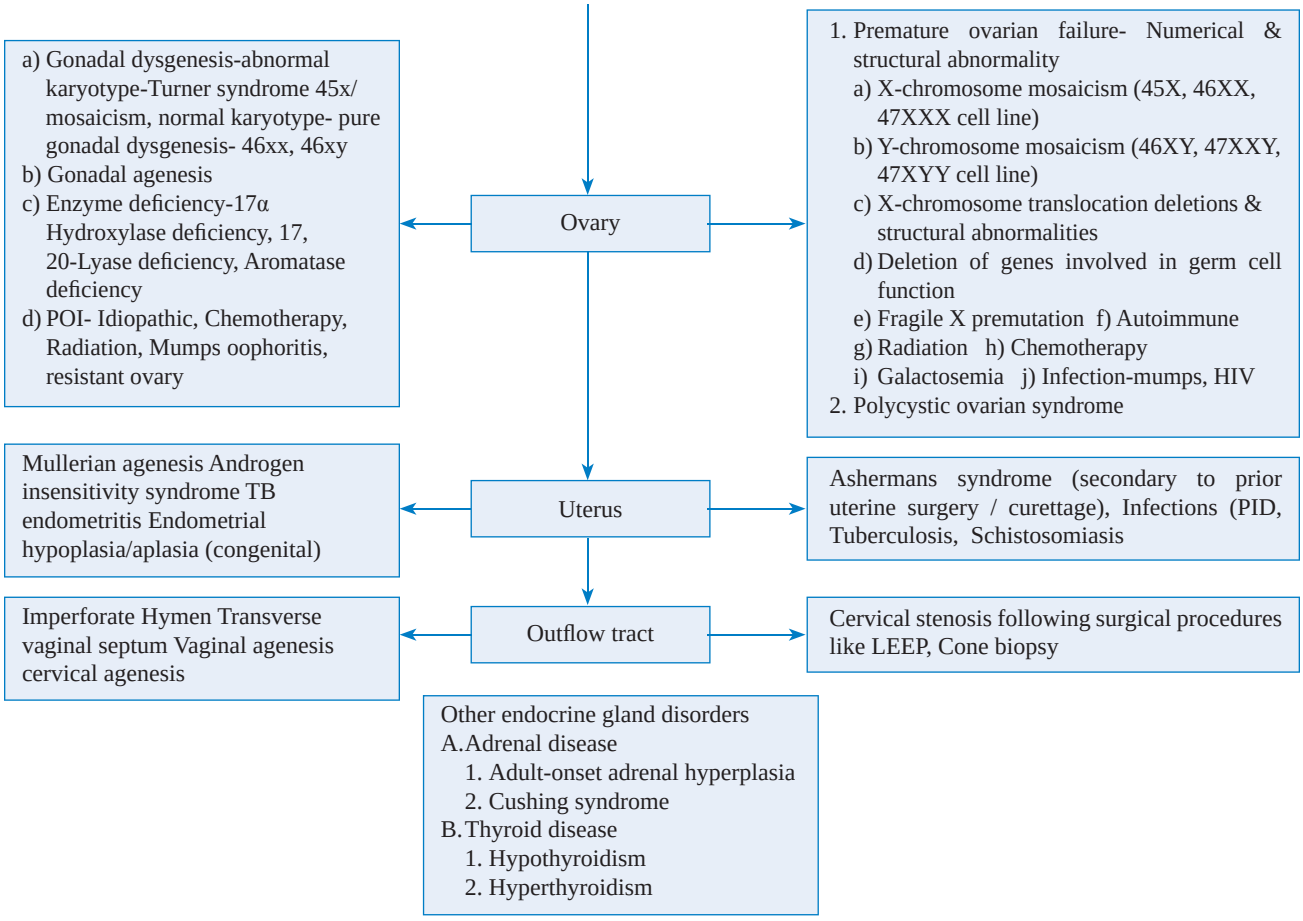
Primary amenorrhea describes patients who have never menstruated, and

Secondary amenorrhea describes those who have menstruated previously but now do not.

With a few exceptions, the causes of primary amenorrhea are similar to the causes of secondary amenorrhea (Fig. 1)

The basic requirements for normal menstrual function includes four anatomically and functionally distinct structural components—(1) the genital outflow tract including the uterus, cervix, and vagina; (2) the ovary; (3) the pituitary; and (4) the hypothalamus —thus providing a natural and useful hierarchy for organizing the diagnostic evaluation of amenorrhea. Causes of amenorrhea can be categorized according to the site or level of the disorder or disturbance[2]





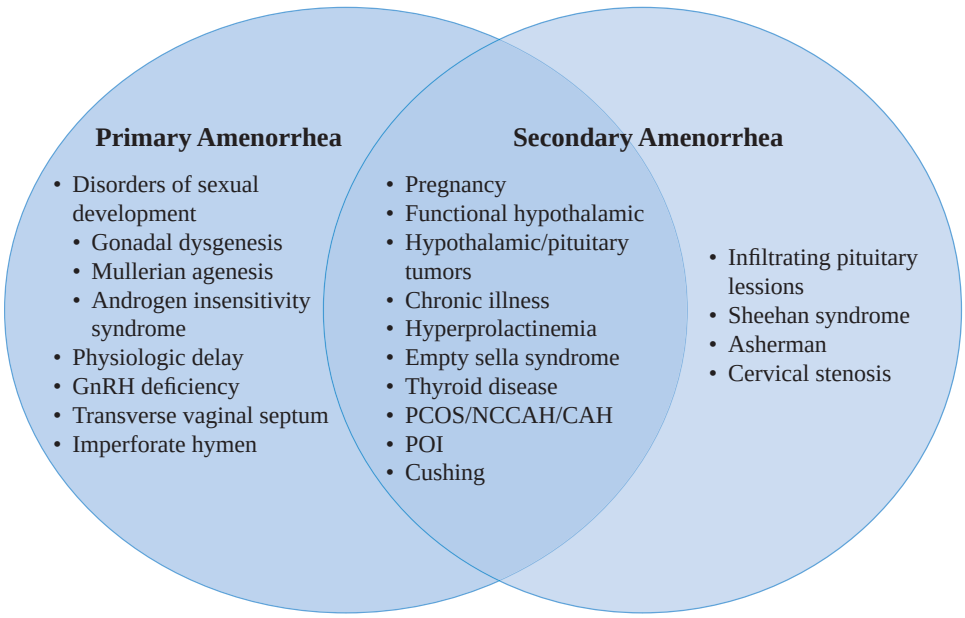


Fig 1: Overlap of causes between primary and secondary Amenorrhea[1]

Evaluation of Amenorrhea

Primary amenorrhea[1,2]

Step 1- HISTORY-

1. H/o completion of other stages of puberty- growth spurt, development of axillary and pubic hair, breast development.- ovarian or pituitary failure or chromosomal anomaly
2. Family h/o delayed or absent puberty- familial disorder
3. What is her height relative to family members- short stature may indicate TURNER SYNDROME

OR HYPOTHALAMIC-PITUTARY DISEASE.

4. H/o Neonatal or childhood health problems- Neonatal crisis may suggest CAH
5. Symptoms of virilization- Acne, hirsutism, deepening of voice etc.- PCOS/ androgen secreting ovarian or adrenal tumor.
6. H/o stress, change in weight, diet or exercise habits or illness- Hypothalamic amenorrhea
7. H/o any drug intake that might cause amenorrhea - phenothiazines, reserpine derivatives, amphetamines, benzodiazepines, antidepressants, dopamine antagonists, opiates can cause hypothalamo-pitutary dysfunction.
8. H/o any drug intake like hormones leading to development of breast
9. H/o Galactorrhea (h/o drugs like metoclopramide, antipsychotics)
10. Symptoms of other hypothalamo-pitutary disease including headches, visual field defects, fatigue, or polyuria and polydipsia?
11. Cyclical pelvic or lower abdominal pain or urinary complaints- Cryptomenorrhea
12. H/o exposure to tuberculosis, radiation or chemotherapy in childhood

Step 2 : Physical examination-

1. Height, weight, BMI and arm span (normal arm span for adults is within 5 cm of height)
2. Breast development- Tanner stage, axillary hair- present/absent
3. Abdominal examination - inguinal area- lump-s/o testis, enlarged uterus- hematometra
4. Genital examination- Pubic hair- Tanner staging, clitoral size, hymen, depth of vagina and presence of cervix, uterus and ovaries (mainly by pelvic ultrasound) by gentle one finger examination or rectal examination.
5. Hirsutism, acne, striae, increased pigmentation
6. Classic physical features of Turner syndrome- low hair line, web neck, shield chest and widely spaced nipples, blood pressure both arms- coarctation of Aorta

Step 3: Basic laboratory testing- depends on findings of physical examination whether Mullerian structures are present or absent-

1. pelvic ultrasound - presence of uterus, cervix and ovaries
2. if uterus absent- karyotype, serum testosterone, FSH, LH- (46 XX, normal female testosterone levels e, normal FSH- Mullerian agenesis/ 46 XY, normal male testosterone levels, normal FSH- Androgen insensitivity syndrome (AIS)/ 46XY/46 XX, normal female testosterone, high FSH- Gonadal dysgenesis) - Y chromosome material increases the risk of Gonadoblastoma in dysgenetic gonads- gonadectomy recommended in AIS after puberty and immediately on diagnosis in Swyer syndrome.
3. If uterus present and outlet obstruction ruled out- HCG (rule out pregnancy/ S.TSH/S.prolactin/ FSH

Secondary amenorrhea[1,2]

Step 1:- Rule out pregnancy- UPT/hCG

Step 2: History-

Apart from the points in history as in a case of primary amenorrhea following should be noted

1. Age at menarche. Menses preceding amenorrhea – regularity/ amount
2. H/o preceding dilatation curettage or other uterine surgery
3. H/o obstetrical events-lactation, massive PPH (Sheehans syndrome), dilatation and curettage
4. H/o chronic illness such as diabetes, renal failure (which is often associated with elevated prolactin levels, primarily reflective of altered renal clearance), or inflammatory bowel disease, previous head trauma, tuberculosis.
5. H/o time and duration of any treatment with oral contraceptive pills, progestins (e.g., depot medroxyprogesterone acetate [MPA], progestin implants, or intrauterine system), GnRH agonists or drugs that can affect central neurotransmitter secretion and thereby disrupt hypothalamopituitary signals that are critical to normal menstrual function (phenothiazines, reserpine derivatives, amphetamines, benzodiazepines, antidepressants, dopamine antagonists, opiates)
6. Family history- autoimmune disorders, spontaneous POI or intellectual disability

Step 3: Physical examination

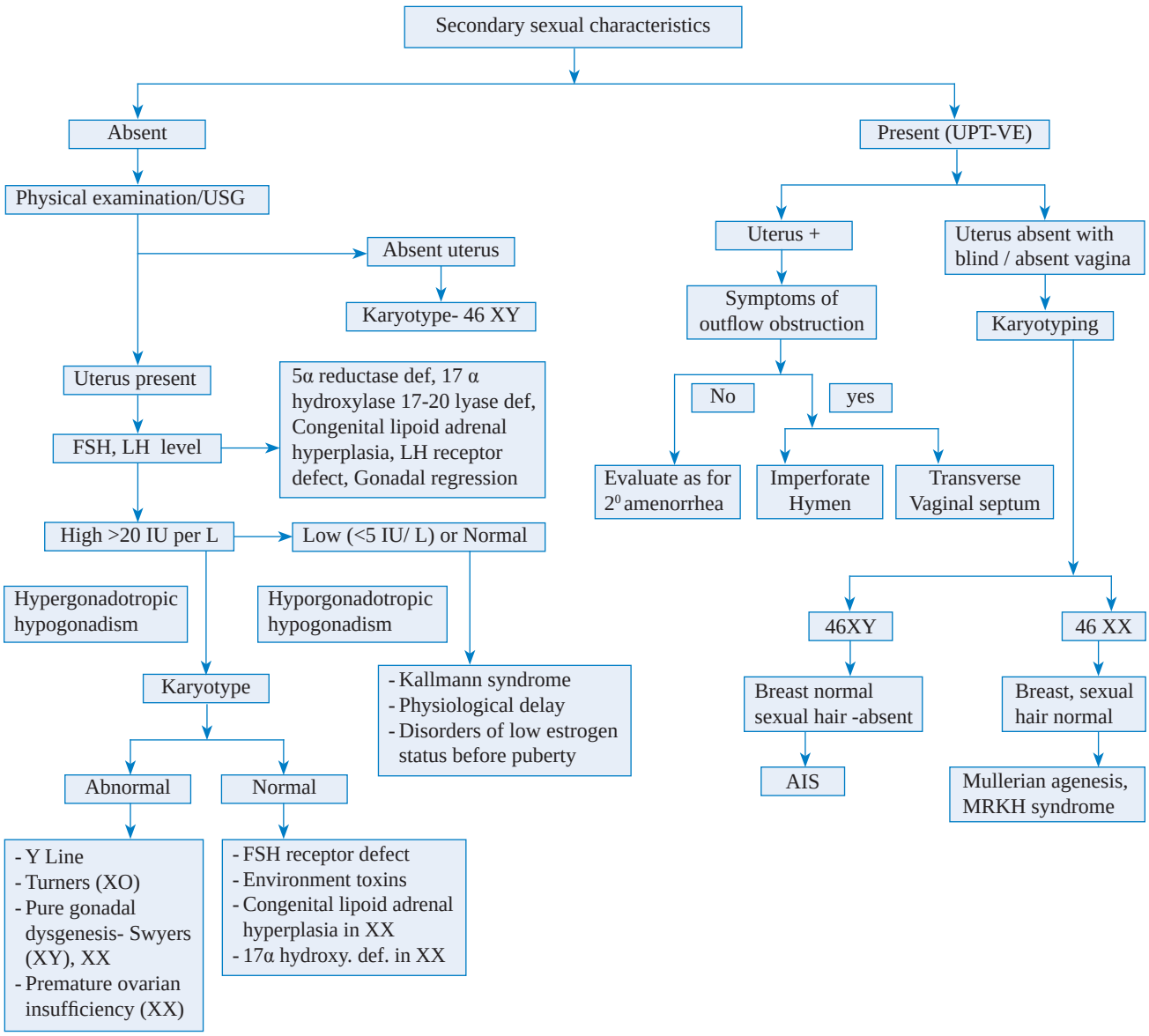
1. Height, weight, BMI
2. Skin- soft, warm, moist with rapid pulse, fine tremor, hyperreflexia- hyperthyroidism. Coarse, dry skin, slow pulse, diminished reflexes, thinning of hair- hypothyroidism

3. Hirsutism, acne, striae, acanthosis nigricans
4. Parotid gland swelling and/or erosion of teeth enamel- eating disorder (bulimia nervosa)
5. Breast- galactorrhea, atrophy

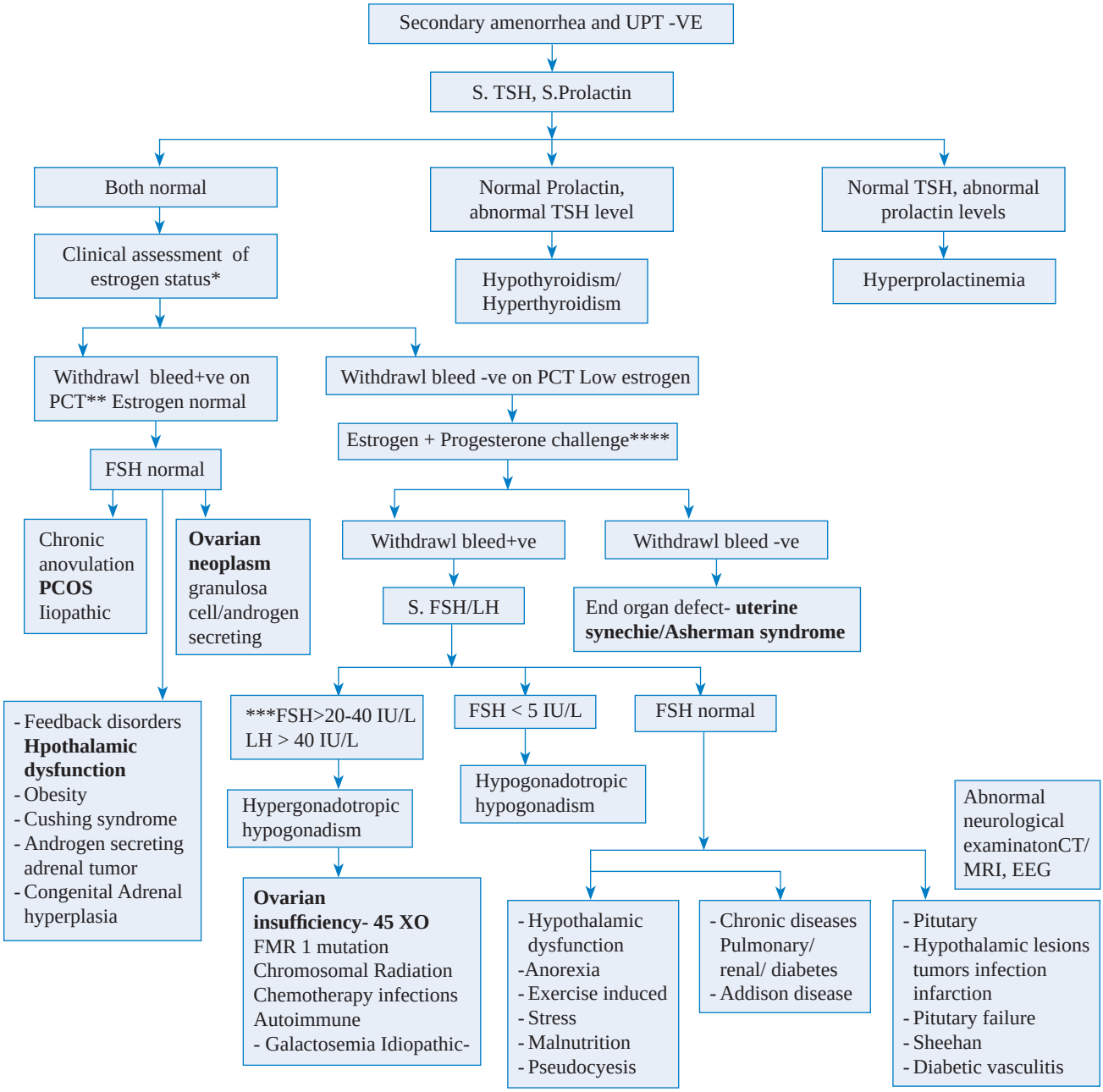
Step 4: Basic laboratory tests-

Apart from Urine pregnancy test or HCG to rule out pregnancy minimal laboratory testing should include serum prolactin, TSH and FSH. If clinical evidence of hyperandrogenism- - serum total testosterone, 17-hydroxyprogesterone (if high risk) to rule out non classic 21-hydroxylase deficiency and dehydroepiandrosterone sulfate (DHEA-S) to look for adrenal source of androgens. Serum total testosterone >200 ng/dl, DHEA-S> 380µg/dl- evaluate for androgen secreting adrenal or ovarian tumors by imaging studies. Serum total testosterone >80 <150 ng/dl- PCOS.

Evaluation of Primary Amenorrhea-Algorithm[1]



Evaluation of Secondary Amenorrhea[1]



***** h/o vaginal dryness or hot flashes, serum estradiol level > 40 pg/mL (inter assay discrepancies often exist and serum estrogen levels can vary greatly on a day-today basis), Vaginal ultrasound demonstrating a thin endometrium (other reasons for non functional endometrium ruled out), **progestogen challenge test**-little utility in routine performance (False positives and false negatives are common).[1,4,5]

** PCT- progesterone challenge test- tab medroxyprogesterone acetate 5-10 mg for 7-10 days.

*** FSH levels should be repeated after 1 month for confirmation of POI.

**** E+P challenge- Tab Conjugated equine estrogen 0.625 mg once a day x 21 days+ tab medroxyprogesterone acetate 10 mg once a day for the last 10 days

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Adolescent Polycystic Ovary Syndrome - Still an Enigma!

Megha Mittal[1], Pratima Mittal[2]
[1]Senior Resident, [2]Professor, VMMC & Safdarjung Hospital, New Delhi

Polycystic Ovary Syndrome (PCOS) is a heterogenous syndrome of unknown aetiology and is a leading cause of anovulatory endocrinopathy. PCOS of late has taken an epidemic form with a prevalence of 8% - 13% in women of reproductive age[1,2]. The diagnosis and management of adolescent PCOS is different in adolescent from that of adults. To address the queries and gaps this article summaries the diagnosis and management in adolescent PCOS after reviewing the recent guidelines.

Adult v/s Adolescent PCOS – Diagnostic Challenges

These can be considered two different entities because targeted areas and outcomes of priority in these two phases of life are different.

The Rotterdam criteria used in diagnosis of adult PCOS requires at least 2 of 3 features[3].

1. oligo-anovulation
2. Clinical/Biochemical evidence of hyperandrogenism
3. Polycystic ovaries on ultrasound.

However diagnosis of adolescents PCOS has stronger focus on clinical features like irregular menses, acne, hirsuitism and alopecia. Adolescent PCOS is difficult to diagnose as 85% of menstrual cycle are anovulatory during early post menarchal years. Even after 3 years; 50%of cycles are anovulatory. Acne is common in adolescent irrespective of PCOS and hirsuitism associated with PCOS develops later. Polycystic ovaries are often a normal finding in adolescence because of multifollicular development.

The ESHRE/ASRM sponsored 3rd PCOS consensus group (Amsterdam 2010) concluded that the diagnostic criteria for adolescent PCOS should be different from that in adults with focus on treatment of individual manifestations and surveillance of high risk group such as those with hirsuitism, irregular cycles and obesity [level B] [5]

ESHRE/ASRM 2018 set up evidence based guidelines for diagnosis and treatment of PCOS[6]. They proposed that the diagnosis of PCOS in adolescence should have stronger focus on clinical features; limited indications of ultrasonography; and simpler tests for biochemical hyperandrogenism.

For diagnosis of PCOS they opined that[6]:

A) Menstrual cycles should be considered **abnormal in adolescents** if :

- First year post menarchal any one cycle >90 days is abnormal.
- 1 to <3 years post menarche <21 or >45d.
- More than 3 year post menarche to perimenopause <21 to>35 or < 8cycles/year.
- Primary amennorhoea by age 15 to >3 years post thelarche.

NOTE:- Adolescents who don't meet the diagnostic criteria and are at "increased risk" (obesity hirsuitism, H/o diabetes and PCOS in family) should be reassessed after 8 years post menarche[7].

B) Biochemical/Clinical hyperandrogenism

- Clincal hyperandrogenism

  Should be reported in the presence of acne, alopecia and hirsuitism. Reported unwanted excess hair growth /alopecia should be considered important regardless of severity. Assess hirsutism using modified Ferriman Gallwey score (mFG) with a level ≥ 8 indicating hirsutism. The Ludwig visual score is used for assessing the degree and distribution of alopecia

- Biochemical hyperandrogenism

  Should be assessed by calculated free androgen index (FAI) using values of total testosterone and SHBG. Direct levels of free testosterone should not be measured in view of poor sensitivity and unreliable accuracy. DHEAS and Androstenedione can be considered if total/free testosterone is not elevated.

C) Polycystic appearing ovaries on USG

USG should not be used for diagnosis of PCOS with gynaecological age <8years i.e. less than 8 years post menarche because of multi follicular development at this stage[6]. However it should be done to rule out other pathologies.

- In most adolescents TAS is done because they are sexually inactive; herein the diagnosis of Polycstic Ovary Morphology (PCOM) is best focused on ovarian volume with a threshold of ≥ 10ml.
- Transvaginal USG approach is preferred in diagnosing PCOS, if sexually active.
- TVS (frequency bandwidth 8 MHz) on either ovary follicle number >20 and/or an ovarian

volume ≥ 10ml (Absence of corpora lutea, cyst or dominant follicle)

- If <8MHz frequency for PCOM-an ovarian volume ≥ 10ml on either ovary

Investigations

Investigation required for diagnosis and management of PCOS are tabulated under Table 1

Table 1: Investigations for diagnosis and management of PCOS

Essential investigations	Desirable investigations
• Serum TSH & Serum prolaction	• Serum Androstenedione
• 17 OH progesterone	• FSH/LH
• 2 hr 75 gm OGTT	• Fasting Insulin levels
• Lipid profile	• Vitamin D3
• Calculated free Testosterone	• Free Testosterone
• Free Androgen Index	
• Ultrasonography (TVS/TAS) to rule out other pathologies/for diagnosis	
Screening be done for Obstructive Sleep Apnea[8] Emotional well being, Eating Disorders and Body Image Issues Assess Quality of Life	

Screening for Metabolic Disorders

Since PCOS is associated with metabolic issues in adult life therefore screening for these conditions and lifestyle modifications are an integral part of the management. Adolescent PCOS should be screened for the following conditions

A. Insulin resistance and obesity: -

Height; weight and ideally waist circumference should be measured and BMI calculated OGTT/ HbA1c should be measured every one to three years.

B. Hypertension: -All women should have Blood pressure measured annually.

C. Hyperlipidemia: -All obese and overweight women should have fasting lipid profile.

D. Obstructive sleep apnea: - Is very commonly associated with PCOS and its metabolic dysfunctions. Hence screening for OSA through a simple screening tool eg. Berlin's questionnaire is recommended[8,9].

E. Emotional well-being:-anxiety and depressive symptoms should be routinely screened in all adolescents.

F. Body image issues:- Negative body image issue should be screened by using questionnaire.

G. Eating habits:- SCOFF tool can be used for screening.

H. Quality of life: -modified (PCOS Q) may be useful clinically to highlight PCOS features.

Treatment modalities based on ESHRE 2018 guidelines[6]:

Holistic approach for management of PCOS is required and pharmacological therapy in PCOS needs to be considered along with health education, lifestyle modifications and other options including cosmetic therapy and counselling. Objectives of management in adolescent PCOS are treatment of menstrual Irregularity; management of hirsutism, alopecia and acne i.e **individual PCOS manifestations in adolescents should be treated**. Another important goal is to reduce the far reaching consequences of insulin resistance and glucose intolerance as well as development of metabolic syndrome in these cases by inculcating good life style measures.

A. Lifestyle measures- This is advocated as initial management and as an adjuvant with any other modality:

- Diet – Achievable goals such as 5% to 10% weight loss in those with excess weight yields significant clinical improvement
  - Overweight and obese: Advocate an energy deficit of 30% or 500 - 750 kcal/day (1,200 to 1,500 kcal/day)
  - Individualized approach for tailoring of dietary changes: consider food preferences, avoid unduly restrictive and nutritionally unbalanced diets
  - Reduce carbohydrate to only 40% of total calories (130gms/d)
  - 3 main meals / 3 snacks
  - Avoid refined carbohydrates and sugars in processed foods
  - Increase fibre content in diet by increasing fruit and vegetables / oat bran / barley
  - Increase of intake of omega 3/6 fatty acids – fish / nut / olive oil
  - Never skip breakfast / meals. Eat breakfast within 2 hours of waking up.
- Exercise –
  - **For modest weight-loss**, prevention of weight-regain and greater health benefits- A minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensity or an equivalent combination of both, and muscle strengthening activities involving major muscle groups on 2 non-consecutive days/ week
  - **For maintaining healthy lifestyle**- At least 60 minutes of moderate to vigorous intensity physical activity/ day, including those that strengthen muscle and bone at least 3 times weekly

    Activity to be performed in at least 10-minute

bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days. Minimized sedentary, screen or sitting time.

B. Pharmacotherapy

1. Treatment of irregular cycles and hisuitism

Combined oral contraceptive pills:

- First line pharmacotherapy in adolescents PCOS for clinical hyperandrogenism and irregular cycles is combined oral contraceptive pills.
- **Specific types** or dose of progestins, estrogens or combinations of COC **cannot** currently be recommended in adolescents with PCOS
- Various OCP's have similar efficacy eg. Mala N which is freely available in government hospital is equally effective and can be considered as first line treatment.
- Low dose estrogen (20/30 eg EE) containing OCP's are preferred.
- The 35 microgram ethinyloestradiol plus cyproterone acetate preparations should not be considered first line in PCOS due to adverse effects including venous thromboembolic risks.

Antiandrogens:

- Antiandrogens should be considered in PCOS if OCPs and metformin have failed to improve outcomes in androgen related alopecia and hirsuitism.
- Spironolactone- androgen receptor blockade, 100-200mg/day in two divided doses
- Cyproterone acetate- androgen receptor blockade, used with E2 as OC pill
- Flutamide- competitive inhibitor of androgen receptor, 125 to 250 mg twice daily
- Finasteride- 5 alpha reductase inhibitor, 5mg daily
- **Wait for at least 6 months for the response, if response is seen continue treatment for further six months or may be for years**

2. Treatment of insulin resistance

Metformin

- It should be considered in women with PCOS with BMI > 25mg/m2, where COCs and lifestyle measures do not achieve the desired goals.
- Metformin may offer greater benefit in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups
- Metformin lowers blood glucose by inhibiting hepatic glucose production & enhancing peripheral glucose uptake
- Should be started at low dose of 500mg with increments 1-2 weekly, 6 months of therapy is required for metabolic outcomes.

Myoionositol

- Naturally existing carbohydrate compound available as diet supplement and plays role in insulin signaling thereby increasing insulin sensitivity.
- Inositol (in any form) can be considered an experimental therapy in PCOS

3. Treatment of obesity

- Should be considered if lifestyle measures and insulin sensitizers fail to improve outcome
- Orlistat and Sibutramine can be given to women with BMI >30.

Conclusion

Diagnosis of PCOS in adolescents differs from that of adults. In Modern medicine, management of any disease should be holistic and should inculcate physical, social and mental wellness. Individual PCOS manifestations in adolescents (eg: obesity, hirsutism and irregular menses) should be treated. They should be encouraged to adopt balanced lifestyle. These early interventions provide a window of opportunity to prevent long-term adverse metabolic outcomes.

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Polycystic Ovarian Syndrome- Long-Term Consequences

Pikee Saxena
Professor, Dept. of Obs. & Gynaecology, Lady Hardinge Medical College & SSK Hospital, New Delhi

Introduction

Polycystic ovarian syndrome (PCOS) is a multisystem endocrinopathy characterized by chronic anovulation, hyperandrogenism and polycystic ovaries on ultrasonography. It affects about 5-10% of premenopausal women. Although 50-70% of women with PCOS are overweight and obese, 30% may be lean. The underlying pathology in both lean and obese women with PCOS is insulin resistance. PCOS has varied presentations like oligomenorrhea, amenorrhea, hirsutism, acne, balding, obesity, acanthosis, infertility, gestational diabetes during pregnancy.

Regardless of age the prevalence of gestational diabetes, impaired glucose tolerance and Type 2 DM are significantly increased in PCOS. About 25% of adolescents with PCOS fulfil the criteria of adolescent metabolic syndrome. PCOS leads to number of long term sequelae like dyslipidemia, diabetes, hypertension, cardiovascular disease (CVD), pregnancy-associated disorders, malignancies, sleep disorders, non- alcoholic fatty liver disease and metabolic syndrome.

Prediabetes and Diabetes

The key underlying abnormality that leads to later development of impaired glucose tolerance appears to be insulin resistance. Markers of insulin resistance are central obesity, acanthosis, hyperandrogenism. Majority of PCOS women have central obesity which is associated with high cardiometabolic risk. Due to the underlying insulin resistance, many of these women are prediabetes defined as fasting plasma glucose between 100-125 mg/dl or impaired plasma glucose levels 2 hours post 75 gm glucose load between 140-199 gm/dl or HbA1c levels between 5.7-6.4%. Furthermore, for all these three values the risk is continuous which is it lesser at lower end of normal range and higher at the upper end of the normal range.

As age increases, insulin resistance becomes worse. Evidence demonstrates that the prevalence of type 2 diabetes in women diagnosed with PCOS is 7 times higher than controls. Insulin resistance combined with abdominal obesity is thought to account for the higher prevalence of type 2 diabetes in PCOS.

Cardiovascular Disease and Hypertension

Hyperinsulinemia appears to be the main reason for the increased cardiovascular risk of women with PCOS. There are two mechanisms by which insulin resistance in PCOS contributes significantly to higher incidence of cardiovascular disease in these women. One mechanism is the direct atherogenic action and the other mechanism is the dyslipidemia. They usually have high concentrations of serum triglycerides, total and low-density lipoprotein cholesterol along with low levels of HDL In addition, serum plasminogen activator inhibitor-I concentrations are also elevated which could lead to impaired fibrinolysis that affects vascular tissue causing changes associated with coronary heart disease. Cardiovascular disease may develop in these women because of endothelial dysfunction, microalbuminuria, proatherosclerotic and inflammatory factors, diabetes, dyslipidemia and hypertension.

Women with PCOS have 4 times higher chances of developing hypertensive disorders during pregnancy than in non PCOS individuals. The prevalence of hypertension is three times higher in women with PCOS between the age of 40-59 years in comparison with controls.

Malignancy

Endometrial Cancer- Prolonged anovulation resulting in endometrial hyperplasia under influence of unopposed estrogens increases the risk of endometrial carcinoma. The known factors which increase the risk of developing endometrial cancer are obesity, long-term use of unopposed estrogens, nulliparity, infertility, hypertension and diabetes. Evidence from a recent study shows that the excess risk of endometrial cancer in women with PCOS was noted to be 3.1 (95% CI, 1.1-7.3).

Ovarian Cancer- Evidence suggests that there is increased risk of ovarian malignancy because of multiple ovulations inductions. A study connecting clomiphene and ovarian cancer suggests that the relative risk for ovarian cancer for women with PCOS is 4.1 compared to controls.

Breast Cancer- There is a positive association between PCOS and the presence of family history of breast cancer. In a study of 217 women, the proportion of women with positive family history of breast cancer was significantly higher in women with PCOS compared with controls

Obstructive Sleep Apnea

The prevalence of obstructive sleep apnea is increased in obese women with PCOS. Androgen levels and insulin resistance are positively associated with obstructive sleep apnea and continuous positive airway pressure (CPAP) therapy improves insulin sensitivity in affected women.

Non-alcoholic Fatty Liver Disease

Ethnicity, increasing age, obesity, hypertension, dyslipidemia and diabetes are risk factors of non-alcoholic fatty liver disease or non-alcoholic steatohepatitis. A 15-60% prevalence of NAFLD is reported in women with PCOS. Diagnosis of NAFLD can be made by non-invasive quantification of fibrosis (ultrasound) or liver biopsy. Consultation with specialists and control of underlying pathology by life style modifications, metformin along with Vitamin E 800mg/day are recommended for treatment.

Psychological and Behavioral Disorders

Women with PCOS are at an increased risk of psychological and behavioral disorders as well as reduced quality of life (QoL). It has been shown that PCOS has a significant detrimental effect on QoL compared with controls and weight issues, hirsutism, acne were most likely to affect QoL in women with PCOS. Women with PCOS are at higher risk of developing psychological difficulties (such as depression and / or anxiety), eating disorders and sexual and relationship dysfunction.

Prevention of Long Term Complications

Efficient management of PCOS provides a prospective window of opportunity to avoid the risk of associated complications. Life style modification is the first line intervention in preventing the development of long term metabolic consequences later on in life. Weight reduction with the aim of optimizing BMI with exercise and dietary modification has been shown to delay or prevent DM in obese and overweight women with PCOS.

In women with prediabetes life style modification in the form of behavior modification, moderate intensity exercise of at least 30 min/day, dietary control is effective.

Behavioral Modification

The key to maintain life style modification is regular enforcement and supervision. It can be done by goal setting, self- monitoring, stimulus control, assertiveness training, slower eating and by reinforcing changes.

Exercise

A goal of mminimum 150 min/week moderate exercise or 75 min of vigorous exercise including muscle strengthening at least 2 times/week on non-consecutive days. Physical activity includes leisure time physical activity, transportation (walking cycling), occupational work, household work, games, planned exercise. Physical activity should have SMART Goals which are Specific, Measurable, Achievable, Relevant, Time limited. Ideal daily 10000 steps including 30 min of structured physical activity (or 3000 steps) should be advocated.

Self- monitoring with fitness tracking devices, technologies for step counting and exercise intensity monitoring are useful adjuncts to minimize sedentary behaviour.

Pharmacological Intervention

In younger women, BMI> 35 kg/m2 or with previous history of gestational diabetes mellitus (GDM) addition of metformin may be considered along with lifestyle modification especially if lifestyle alone is not effective. Metformin is the only drug currently recommended in women with prediabetes but it is less effective than diet and exercise combine. Metformin is started initially as 500mg once a day and then slowly increased weekly in increments of 500mg to the maximum dose of 2gm/ day. B12 supplementation should be given during long term treatment with Metformin.

Screening

Women with PCOS have a significant annual conversion rate to type 2 DM hence regular screening of all women is indicated for recognizing type 2 DM every 1-3 yearly depending on the associated risk factors. Along with 75gm OGTT, BMI, and lipid profile should also be monitored regularly in these women. Screening should be offered to all PCOS women preconception when planning pregnancy or seeking fertility treatment.

Suggested Reading

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Hirsutism

Kusum Lata[1], Alka Kriplani[2]
[1]Assistant Professor, AIIMS, New Delhi, [2]Director, Dept of Minimal Invasive Gynaecology & ART, Paras Hospitals, Gurgaon

Hirsutism is a common clinical condition affecting around 5-10% of the women and is a common presenting complaint in the outpatient department of gynecologist and dermatologist for cosmetic reasons. It is a cutaneous manifestation of androgen excess and is presented as excessive growth of coarse hair in a male pattern distribution on the face and body. Hirsutism is caused either due to an increased production or increased sensitivity of hair follicles to androgens. The various causes can be classified on the basis of site as depicted in Table no 1.

Table 1. Causes of Hirsutism

Cause	Disorder	Prevalence
Ovary	PCOS Hyperthecosis Androgen secreting tumour	**70-80%** **0.5%**
Adrenal	CAH (2-8%) Adrenal tumour (<0.5%) Cushing's syndrome	2-8% 0.5%
Drug Induced	Anabolic steroids, danazol, valproate, phenytoin, minoxidil, glucocorticoid, cyclosporine, progestins, testosterone inj.	
Others	Hypothyroidism, hyperprolactinemia, anorexia nervosa, luteoma in preg, menopause	6%
Idiopathic		5-15%

PCOS is by far the most common cause of androgen excess in women. **Idiopathic hirsutism** occurs in women with regular menstrual cycles and normal serum androgen levels and is mostly due to an increased sensitivity to androgens (mediated by increased peripheral 5α-reductase activity) as improvement in hair growth is seen with the use of 5α-reductase inhibitors.

Postmenopausal women may exhibit hirsutism due to hyperthecosis of ovarian stroma due to stimulation by high postmenopausal gonadotropin conc. or rarely due to presence of ovarian and adrenal tumor.

Evaluation of women with Hirsutism

Evaluation of hirsute women is aimed at quantifying the severity of hair excess and identifying the few having other causes that require additional specific evaluation or treatment (such as hyperprolactinemia, CAH, or androgen-secreting tumors) and should begin with a careful history and physical examination, which always provide important diagnostic clues. Laboratory investigation and imaging are used primarily to exclude other rare or potentially serious possibilities.

Hirsuitism is clinically quantified by a standardized scoring known as **Modified Ferriman Gallwey scoring** which scores 9 of 11 body areas originally proposed excluding lower legs and forearm with a total maximum score = 36 but it it is difficult to use clinically because most women who seek medical attention for the complaint already are using one or more methods of hair removal. Moreover, it has limitations of being subjective in nature, so to minimise bias instruct patient not to epilate or do waxing for atleast 4 weeks and use a uniform graphical/ photographic representation of scoring system.

Table 2. Detailed History

Rate of onset	(gradual/sudden)
Menstrual history	Age at menarche, frequency and regularity of menses(eight or fewer menses per year is consistent with oligoovulation)
Sign and Symptoms	Weight gain,Excess hair fall,deepening of voice,decrease in breast size,Headache, visual disturbance, pain/lump abdomen, galactorrhoea
Drug intake prior to onset	Androgens, danazol, 19 norprogesterone,Minoxidil
Family history	Obesity,infertility,CAH, idiopathic

Table 2. Laboratory Evaluation

Serum Marker	Raised values	Implications
Testosterone	>200ng/ml	Normal to increased in case of benign pathology as PCOS/CAH; definitely raised in malignant tumor of ovary or adrenal.
Dehydroepi androsterone Sulfate (DHEAS)	>700ug/dl	Indicates adrenal cause
17 Hydroxy progesterone	<200ng/dl >200ng/dl, do ACTH stimulation test >1000ng/dl	Excludes the disease CAH (congenital adrenal hyperplasia)
LH/FSH	>3	PCOS
Prolactin	**>25ug/dl**	Hyperprolactinemia due to pituitary tumor
TSH	**0.5-4.5mIU/L**	Primary Hypothyroidism
2 hour GTT with 75 gm glucose	**(140-199 mg/dl)** **(>200 mg/dl)**	Impaired Glucose tolerance Diabetes Mellitus (Indicative of HAIR-AN syndrome)
Pelvic Ultrasonography		PCOD, Ovarian neoplasm
MRI/CT		Adrenal Pathology

Management Algorithm

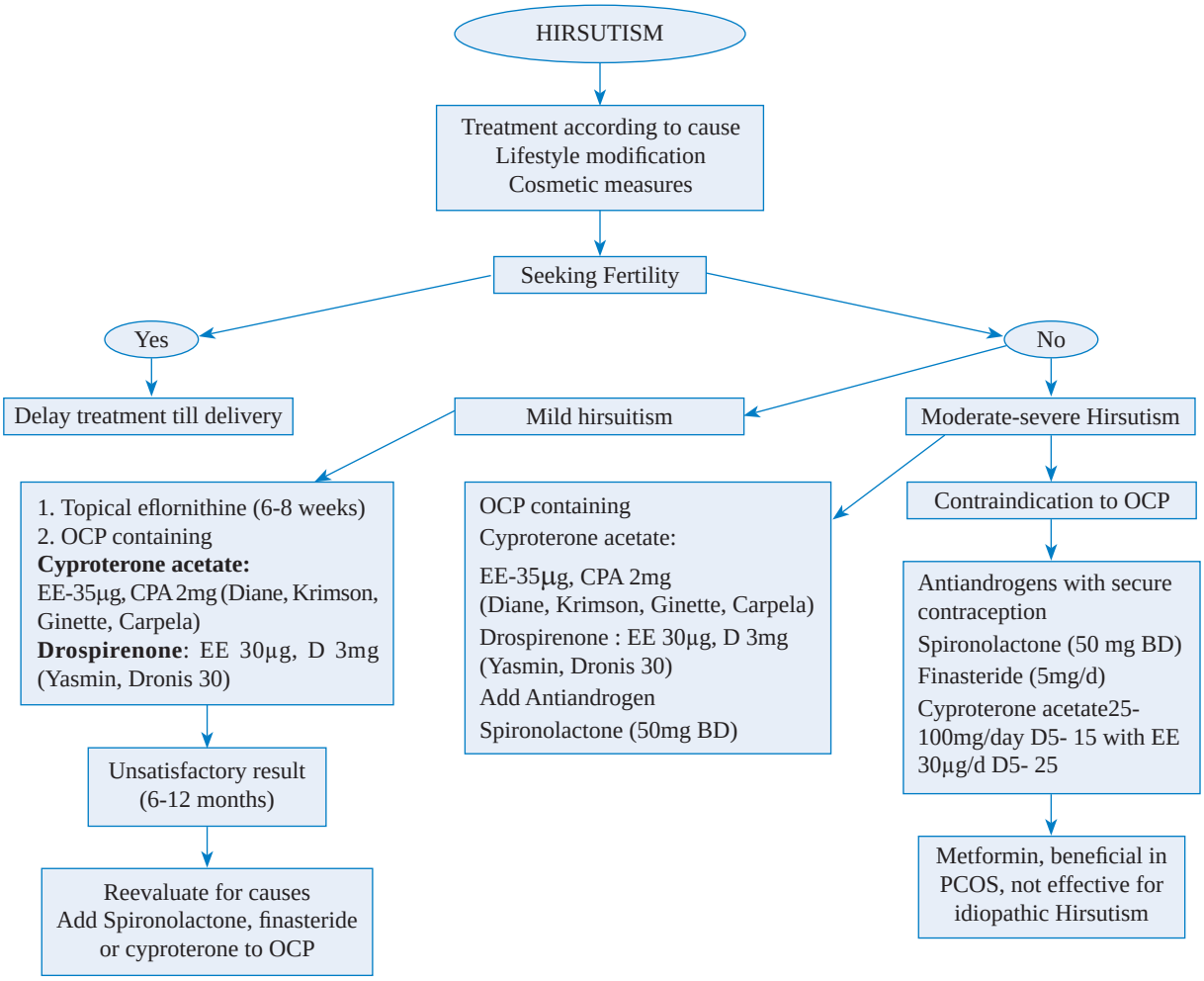

Table 3. Physical examination

Anthropometry	Ht,Wt, BMI, Waist hip ratio, Modified Ferriman Gallwey score
Hyperinsulinemia	Acanthosis nigricans
Hyperandrogenism	Acne, seborrhea, alopecia
Virilisation	Alopecia,decreased breast size, deepening voice,Clitoral hypertrophy
Cushing disease	Striae,moon facies, fragile skin proximal myopathy
Hyperprolactinemia	Galactorrhea

Treatment

Excess facial and bodily hair can be a source of significant psychological stress and treatment should be considered for all women who judge themselves hirsute. In general, treatment, once initiated, should be continued indefinitely or until the time that the patient is ready to pursue fertility because recurrence is seen following treatment discontinuation[3].

Medical Treatment

Serial measurements of serum androgen levels during treatment are neither necessary nor helpful. However, repeated hormonal evaluation is indicated when hirsutism progresses despite treatment.

Cosmetic Approach

Temporary methods include depilation (shaving) or epilation (plucking or waxing) while many prefer electrolysis and photoepilation (laser) which are permanent methods of hair reduction. Topical agents such as eflornithine cream applied twice daily for at least 6 months is usually prescribed.

Key Points

- Manage depending upon etiology and any underlying disorder
- Adrenal or ovarian tumor should be detected promptly if it is rapidly progressive.

- Response to all medical treatments for hirsutism is relatively slow, generally requiring 6 months to achieve significant benefits.
- First choice for hirsutism is a low-dose estrogen–progestin contraceptive and if response is inadequate antiandrogen is added.

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AOGD Sub Committee Nomination (2020-2022)

Nominations are invited for the post of chairperson of the following sub-committee for the year 2020-2022

- ✓ Breast and Cervical Cancer Awareness, Screening & Prevention Committee
- ✓ Infertility Committee
- ✓ Rural Health Committee
- ✓ Multidisciplinary Patient Committee

Eligibility Criteria

1. Person should be a member of AOGD and have at least 10 years standing in the profession with at least 5 years duration of holding senior position in the respective institutions.
2. Chairperson of a subcommittee has to be a member of any subcommittee earlier for at least 1 year.
3. No repeat nomination will be considered after one term of two years.
4. In case of two people applying for the same post, the decision of the executive will be final.
5. In case of any deviation, the decision would be taken by executive committee.
6. Two posts cannot be held by any member at one particular time.

The nominations on plain paper should reach:
AOGD Office: Room No-3080, 3rd Floor, Teaching block, Dept. of Obst & Gynae, All India Institute of Medical Science (AIIMS) by 31st January 2020 along with the bio-data stating the eligibility

Recent Updates in Menopausal Hormone Therapy

Sonali Jain[1], A G Radhika[2]
[1]Senior Resident, [2]Consultant, Department of Obstetrics & Gynecology, UCMS & GTB Hospital, Delhi

Background

A woman spends 40% of her life in menopause. The estimated mean age of menopause is 46 years in India which is lower as compared to Caucasians [1,2,3]. With increase in life expectancy Menopausal Hormone Therapy (MHT) is indicated for treatment of symptoms and prevention of morbidity associated with menopause (Fig 1)

Current Status of Menopausal Hormone Therapy

MHT is considered safe for healthy, symptomatic women who are within 10 years of menopause or less than age 60 years of age and who do not have contraindications to MHT. [4,5,6]

While estrogen-progestin therapy is preferred for women with uterus; unopposed estrogen is the choice for women post-hysterectomy.

Results of Women's Health Initiative (WHI) combined hormone therapy (HT) trialdocumented that risks for use of MHT included CHD events, stroke, venous thromboembolism (VTE), and breast cancer, while benefits included a reduction of fracture and colorectal cancer risk. [7,8,9]

The risk of stroke, VTEand fracture with unopposed conjugated equine estrogen was similar to thatwith combined therapy trial; risk of CHD appears to depend upon the duration of exposure, with no excess risk observed in younger (<60 years of age) menopausal women.

No increase in either CHD or breast cancer risk was observed with unopposed estrogen use (in fact a reduction in breast cancer risk was observed).

Formulations of Menopausal Therapy have listed in this write-up. Availability in India needs to be erified

Hormonal Preparations for MHT

1) Estrogen Options of estrogen preparations are availabletoday are (Tables 1 & 2)

a) Oral estrogens - It includes conjugated equine estrogen, micronized 17-b-estradiol, esterified estrogen, estropipate and ethinyl estradiol. Ethinyl estradiol is the most potent preparation and hence used in very low doses.

b) Vaginal estrogens–Preferred for treatment of genitourinary symptoms. 17-b-estradiol vaginal pessary and vaginal ring are available. Progestin needs to be added for women with uterus.

c) Transdermal estrogen patch- With this route the circulating estrone to estradiol ratio is 1:1 unlike the oral route (3:1) and hence associated with lower risk of thrombosis and stroke. It contains 17-b-estradiol. A transdermal dose of 50 mcg/ day is approximately equivalent to a 0.625mg daily oral dose of conjugated estrogens [10,11].

d) Topical estradiol–Three forms ie lotion, non-aerosol gel and spray are available. It is effective for treatment of vasomotor symptoms. Sprays have been associated with adverse effects in children and pets exposed to drug via skin contact [12].

e) Estrogen depot- Available only in few countries, recommended at 3-4 weekly

f) Low-dose estrogen- Newer in low dose estrogen formulations like transdermal estradiol (0.025 mg/day) or oral estradiol (0.5 mg/day) are beneficial in almost 50% women for relieving vasomotor symptoms. Lower progestin doses are required.

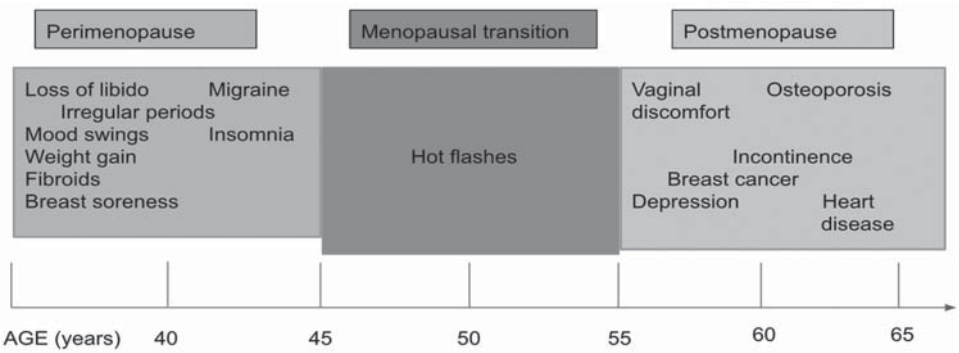

Fig 1. Health effects at menopausal transition

Ultra-low doses of estrogen (transdermal estradiol 0.014 mg/day and oral micronized 17-beta estradiol 0.25 mg/day) also prevent bone loss [13,14] and are effective for hot flashes in some women.

Table 1. Formulations of oral Estrogen

Estrogen preparations	Doses available
Oral estradiol	
Estrace	0.5, 1, 2 mg
Oral esterified estrogen	
Menest	0.3, 0.625, 1.25 mg
Oral estropipate	
Generic (previously available as Ortho-Est)	0.75, 1.5, 3 mg estropipate (equivalent to 0.625, 1.25, 2.5 mg conjugated equine estrogen)
Oral conjugated equine estrogen (CEE)	
Premarin	0.3, 0.45, 0.625, 0.9, 1.25 mg
Oral conjugated synthetic estrogens	
Cenestin	0.3, 0.45, 0.625, 0.9 mg

Table 2. Non -oral estrogen formulations

ROUTE	DOSAGE (mg)
Transdermal	
Estradiol gel	1
Estradiol patch	0.025, 0.0375, 0.05, 0.075, 1
Estradiol spray	0.025
Intranasal	
Estradiol spray	0.15 mg/puff
Subcutaneous	
Estradiol implant	20mg per tablet every 4-8 months
Intramuscular	
Estradiol valerate depot	10mg per depot every 2 weeks
Vaginal	
Conjugated estrogen cream (available in India)	0.625 mg
Dienoestriol cream	0.5 mg
Estradiol cream	0.5 mg
Estriol cream (available in India)	1 mg
Estradiol tablet	0.025 mg
Estradiol ovule	0.5 mg

2) **Progestins**

a) Oral progestins

- Micronised progesterone-It is endometrial protective and has no adverse effects on breast, lipid profile and cardiovascular system [15].
- Medroxyprogesterone acetate- It has been the most common drug prescribed traditionally. It is given in either cyclical (5 to 10 mg/day) or continuous (1.25 to 2.5 mg/day) regime.
- Quarterly progestin regimens-Medroxyprogesterone acetate for 2 weeks in every three months can be used for women who have difficulty tolerating progestin therapy [16,17]. These regimens may be associated with higher risk of endometrial hyperplasia [18].

b) Non- Oral Progestin formulations

- Intravaginal progesterone gelRecent studies suggest that it might be a useful alternative for oral progestins [19,20]. With twice weekly application, it has better compliance.
- Intrauterine device (LNG-IUS)Lowdose LNG-IUS like LNG-14 and LNG-20 are approved for upto three years of use and they are as good as systemic combined estrogen-progestin combinations in preventing endometrial hyperplasia [21,22,23].

2) **Combined estrogen-progestin formulations** (Table 3)

Table 3. Combination MHT formulations

Oral estrogen-progestin combinations	
Prempro	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45/1.5 mg, 0.625/2.5 mg, 0.625/5 mg
Prefest	1 mg estradiol/0.09 mg norgestimate (cyclic)
Activella, Amabelz, Mimvey	0.5 mg estradiol/0.1 mg norethindrone acetate, 1 mg/0.5 mg
FemHRT, Jevantique Lo	2.5 mcg ethinyl estradiol/0.5 mg norethindrone acetate
Jinteli	5 mcg ethinyl estradiol/1 mg norethindrone acetate
Angeliq	0.5 mg estradiol/0.25 mg drospirenone, 1 mg/0.5 mg

Estrogen-progestin patches	
Combi-Patch (twice weekly)	0.05 mg estradiol/0.14 mg norethindrone, 0.05 mg/0.25 mg per day
Climara Pro (weekly)	0.045 mg estradiol/0.015 mg levonorgestrel per day

4) **Other hormonal preparations**

Selective Estrogen Receptor Modulators (SERMs) (Table 4)

- *Tibolone*- It is a progestogen with selective tissue estrogenic and weak androgenic activity; effective in treating vasomotor symptoms, urogenital atrophy and also has protective effect on bone mass. It is less effective than combined estrogen-progestin regimens and is associated with increased risk of stroke [24].
- *Raloxifene*- Has better effect on bone health. It has eight years safety and efficacy. Evidence

supports reduction in the risk of breast cancer [25]. It is less potent antiresorptive agent as compared to alendronate or estrogen [26,27]. It reduces the risk of vertebral fractures but has no effect in reducing non-vertebral fractures [28].

- *Ospemifene*- It was approved by FDA in 2013 for treatment of moderate to severe dyspareunia caused by vulvovaginal atrophy in postmenopausal women [29]. Common side effects include hot flushes, vaginal discharge, muscle spasms and endometrial hyperplasia. [30,31].
- *Bazedoxifene*-Reduces the bone loss thereby the risk of both vertebral and non-verterbral fractures [32]. Its side effects include muscle cramps, nausea, abdominal pain, dyspepsia, diarrhea, oropharyngeal pain, dizziness.

Table 4. SERMS & Dosage

Drugs	Dosage
Tibolone	2.5 mg/day
Raloxifene	60mg/day
Ospemifene	60 mg/day
Bazedoxifene	20-40 mg/day

5) **Alternatives to MHT**

a) Selective Serotonin Reuptake Inhibitors Venlafexine, Paroxetine, Citalopram. Only Paroxetine is FDA approved for menopausal symptoms. They alleviate vasomotor symptoms like hot flushes[33]. Their benefits are balanced against side-effects like nausea, headache, diarrhoea etc.

b) Clonidine- Centrally active □ agonists have been effective in some clinical trials. It improved vasomotor symptoms specially in breast cancer survivors.

c) Pollen extracts- The purified cytoplasm of pollen extract PI82/GC Fem is extracted from monocultures. It inhibits serotonin reuptake and reduces vasomotor symptoms, fatigue and irritability significantly [34].

d) CRE (Cimicifuga racemose)- It is also called as snakeroot and decreases serotonin reuptake. It has been used commonly by German clinicians for treatment of hot flushes. It can be used in women with history of breast cancer [35].

e) Phytoestrogens - These are nonsteroidal compounds that occur naturally in many plants, fruits and vegetables. They have both estrogenic and antiestrogenic properties. There are three main types of phytoestrogens: isoflavones, coumestans and lignans. Two types of isoflavones - genistein and daidzein are found in soybeans and are most potent estrogens of the phytoestrogens. May be prescribed in women with history of breast cancer [36].

New Formulations of MHT

1) Bazedoxifene+ Conjugated estrogen- It is available in Europe for treatment of vasomotor symptoms in women with intact uterus and in United states also for prevention of osteoporosis. Low doses of bazedoxifene (10 or 20mg) with 0.45 or 0.625 mg of conjugated estrogen significantly improved vaginal atrophy and reduced the daily number of hot flushes [37]. It is contraindicated in women who have history of thromboembolic disease, breast or uterine cancer, unusual vaginal bleeding or liver disease.

   Its effect on risk of breast and ovarian cancer is not known.

2) Bioidentical hormones- The term "bioidentical hormone" technically refers to a hormone with the same molecular structure as a hormone that is endogenously produced (eg, 17-beta *estradiol*) and are derived from soy and plant extracts. Used as custom-compounded multihormone regimens (pills, gels, sublingual tablets or suppositories [39]. There are no randomized trials that have determined the efficacy, safety or adverse effects of these preparations.

Table 5. Ready Reckoner For MHT

Risk Factors	Drug of Choice
Thromboembolism	Transdermal estrogen with micronised progesterone
Cardiovascular diseases or stroke	Didrogesterone
Endometrial cancer	Medroxyprogesterone acetate
Breast cancer	Micronised progesterone
Diabetes mellitus	Tibolone
Obesity	Transdermal estrogen
Hyperlipidemia	Transdermal estrogen

Sample Prescriptions for MHT

1) Premenopause

   Transdermal 17- b-estradiol 0.05 mg/day (30 days for 3 months and reevaluate)

2) Perimenopause

   Oral micronised progesterone 200 mg/day (14 days/month)

   LNG-IUS (if not able to tolerate oral progestins)

3) 10 years postmenopausal
   Transdermal estradiol patch 0.05mg/day
   Tab calcium 500mg OD
4) 20 years postmenopausal
   Vaginal estrogen cream 0.5mg/day
   Tab calcium 500mg BD

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- QI Workshop on 14th December, 2019 at All India Institute of Medical Science(AIIMS) under the aegis of Quality Improvement Sub-committee AOGD.

- Group Discussion.

- A CME organized by FOGsd with FOGSI, AOGD, NARCHI and ISCCP on 17th December, 2019 at Madhuban Hotel, GK1.



- Monthly Clinical Meeting on 27th December, 2019 at Sir Ganga Ram Hospital, New Delhi.



- GURUKUL CLASSES on 3rd & 4th January, 2020 Organized by Institute of Obstetrics & Gynecology, Sir Ganga Ram Hospital, New Delhi. Under the aegis of ISOPARB, FOGSI, ICOG & AOGD.

- A CME on 5th January, 2020 at Le Meridian, New Delhi, Under the aegis of AOGD.

XY Females: A Primer for Gynecologists

Deepti Goswami[1], Mrinalini Dhakate[2]
[1]Director Professor, [2]Postgraduate Student, Obstetrics & Gynecology, Maulana Azad Medical College, New Delhi

The gender of an individual is determined by the karyotype, the gonads (ovaries or testes) and the phenotype or genital sex. Discordance between these three determinants leads to disorders of sex development (DSD).

Women, who carry XY chromosome instead of XX, (46, XY DSD) constitute a unique category of DSD that occur due to mutations affecting development of gonad or synthesis or function of testosterone. They usually present with primary amenorrhea or uncommonly, with signs of virilization at puberty. A few of these disorders may present at birth with ambiguous genitalia when they are managed by pediatricians.

The two most common causes of 46 XY female are:

- Androgen insensitivity syndrome (AIS)
- Gonadal dysgenesis (Swyer syndrome).

In a Danish study, out of 124 subjects with 46,XY DSD, 78 had AIS and 25 had gonadal dysgenesis.[1]

Due to rarity of 46, XY DSD, the estimates of prevalence rates are provided by the few studies that covered large population with karyotype analyses. One such study from Denmark estimated the prevalence of 46,XY females to be 6.4 per 100 000 live born females. The figures were 4.1 per 100 000 for AIS and 1.5 per 100 000 for gonadal dysgenesis.[1]

How to diagnose

- Examination - Tanner stage, signs of virilization, patency of vagina, presence or absence of uterus
- Hormonal evaluation
- Imaging of the pelvis to assess genital tract
- Karyotyping
- Genetic testing to identify specific mutations
- Biochemical evaluation of urinary steroid excretion (urinary steroid profile) in rare enzymatic deficiencies
- Histopathology of gonad

Issues to be addressed

- Disclosure of diagnosis and psychological support
- Achieving normal pubertal changes and menstruation
- Fertility
- Need for gonadectomy
- Surgery for correction of virilizing features and construction of vagina
- Bone health and long-term care
- Implication for family members –carriers and other affected individuals

Androgen Insensitivity Syndrome

This condition was first described by John Morris in 1953, who named it testicular feminization syndrome.[2] The condition arises due to mutation in gene encoding for androgen receptors which are expressed in various tissues of the body.[3] Several hundred of such mutations are described. Due to defective receptor, the androgen action on target organ cannot take place despite adequate levels of serum testosterone (peripheral resistance to hormone).

The gene for androgen receptor is located on X chromosome. The disorder has recessive mode of inheritance. So if a woman carries mutation in androgen receptor, some of her daughters will be the carriers of the mutation and the 'sons' who inherit affected X chromosome present with AIS. Sometimes the mutations appear de novo and there is no family history.

Most of the cases have **complete AIS (CAIS)** where androgen receptor function is completely absent. The affected individuals have functioning but non-descended (in abdomen) or partly descended testes (in inguinal canal). Their serum testosterone is in the range for normal adult males. They have female external genitalia since there is no development of scrotum and penis that normally occurs under the influence of testosterone during the fetal life. The Sertoli cells of the functional testes produce anti- mullerian hormone that causes disappearance of Mullerian tract during fetal life. Thus these individuals are born with no uterus or fallopian tube and have a blind vagina. At puberty, the increased levels of testosterones are partly converted to estrogen by aromatase enzyme. This leads to breast development. However, pubic and axillary hairs do not appear, as testosterone does not act at the target tissue due to defective androgen receptors.

The diagnosis can be suspected in a girl child with inguinal swelling or hernia. Most of the times the condition goes undetected in childhood and medical

consultation is sought for primary amenorrhea. Rarely the affected person may present with pelvic mass due to malignancy of the gonad.

When these women present with primary amenorrhea, the diagnosis is made on the basis of clinical examination (absent sexual hair, well developed breasts, blind vagina) and confirmed by serum testosterone levels in male range and 46, XY karyotype. Serum FSH and LH are mildly elevated. Pelvic imaging shows absence of uterus and undescended gonads. MRI may further help to localize the gonads and study precise anatomy of the genital tract. The common differential diagnosis is that of Mayer-Rokitansky-Kuster-Hauser syndrome. However the latter group of women has normal adult pattern pubic and axillary hair, 46,XX karyotype and serum testosterone levels in normal range for females.

The disclosure of diagnosis of AIS should be done in most sensitive manner so as not to disturb their gender identity.[4] Family history when tracked, often reveals other likely affected individuals in the family.

Absence of uterus and vagina becomes a cause of immediate concern. The patient and the parents need to be explained that menarche will not be achieved. Adequate vaginal length can be achieved by vaginoplasty procedure or non-invasively by regular use of dilators.

There is a small risk (1-3%) of development of malignancy in the mal-descended testes. Therefore once adequate breast development is achieved, patient is offered gonadectomy that is usually done laparoscopically.

Once gonads are removed, there is need for hormone replacement therapy.[5] These women need long term estrogen replacement for maintenance of bone health. Since uterus is absent, progesterone is not needed. Estrogen replacement is done with daily administration of conjugated equine estrogen 0.625 mg or estrogen valerate 2 mg or transdermal estrogen 50 µg. This replacement is needed till the age of 50 years. Testosterone supplementation has also been used for some women.[6]

Fertility remains a tricky issue as these women have no oocytes and no uterus. It has been suggested that germ cells from their testes be used for fertility purpose but that would be fraught with much ethical dilemma.

Some of the affected individuals have **Partial AIS (PAIS),** where androgen receptor function is partly present. This situation is more disruptive for gender identity. Clinical presentation will depend on degree of responsiveness of androgen receptors.

The affected individuals may present with ambiguous genitalia at birth. There are several other causes of ambiguous genitalia. Diagnosis of PAIS is based on identification of mutation in androgen receptor gene, which is often difficult to get. Most of the newborns with ambiguous genitalia due to PAIS are raised as males. If female sex is assigned at birth gonadectomy is done well before puberty to prevent virilization. Also, the risk of germ cell tumors developing in testes is higher in PAIS than in CAIS. Vaginoplasty is also needed. Estrogen replacement is done for induction of pubertal changes and continued till the age of 50 years.

Pure Gonadal Dysgenesis (Swyer Syndrome)

The condition, first described in year 1955, occurs due to deletion in sex determining region (SRY) gene on Y chromosome (up to 20% cases) or mutations in other testis-determining factor. Due to these mutations, testis does not develop and gonad is dysgenetic (streak gonad). There is no production of testosterone or anti-mullerian hormone. As a result, the external genitalia are of a female and the mullerian structures persist as uterus, fallopian tube and vagina.[7,8]

The condition goes undiagnosed till the time of puberty, when the patient presents with lack of pubertal development and primary amenorrhea.

On clinical examination there is no breast development or sexual hair development, vagina is patent and imaging reveals small uterus. Their hormonal profile is suggestive of hypergonadotropic hypogonadism, i.e. raised serum FSH, LH and low serum estradiol. Karyotype of 46, XY clinches the diagnoses. There is not much benefit in identifying the causative gene mutation. Majority has no family history of the condition.

The dysgenetic gonads in this condition have 20- 30% chance of developing malignancy (gonadoblastoma, dysgerminoma). Hence early gonadectomy is recommended. Pubertal changes are achieved by hormone replacement therapy with low, incremental doses of estrogen and progesterone is added later to induce menstrual bleeding.

Both CAIS and Swyer syndrome results in taller individual as compared to normal 46 XX women. Women with Swyer syndrome have been reported to be taller and have lower bone mineral density as compared to those with CAIS.[9] This could be due to more profound hypoestrogenemia in Swyer syndrome.

Women with Swyer syndrome require both estrogen and progesterones for hormone replacement, as uterus is present. The treatment is given till the age of natural menopause, i.e., 50 years.

Pregnancy can be achieved through donated oocytes. Successful deliveries, both vaginal and cesarean, with good neonatal outcome are reported since 1988.[10]

Other 46, XY DSD

These are rare conditions and occur due to mutations affecting gonadal development, or affecting testosterone synthesis or function.

- Disorders of testosterone biosynthesis or function- 17 β - hydroxysteroid dehydrogenase deficiency and 5-alpha reductase deficiency. More rare are- LH receptor defects (Leydig cell hypoplasia), 17-alpha hydroxylase deficiency, 17,20 lyase deficiency and P450 oxidoreductase deficiency.
- Mutations in genes affecting gonadal development - WT1 (Denys Drash syndrome, Frasier syndrome), SOX9 (campomelic dysplasia).
- Ovotesticular DSD with 46, XY karyotype

5-alpha reductase deficiency and 17 β - hydroxysteroid dehydrogenase deficiency may present with virilization at puberty manifesting with excessive body hair, clitoromegaly and deepening of voice. However, a majority present with ambiguous genitalia at birth. Uterus is absent as testes produces anti-mullerian hormone. The differential diagnosis includes Partial AIS.[11]

Denys Drash syndrome and Frasier syndrome are attributed to mutations in Wilms tumor gene (WT1) gene and are associated with renal diseases.[12]

The diagnosis of these enzymatic and genetic disorders is challenging and requires inputs from endocrinologists and geneticist and also special investigations like urinary steroid profile.

Due to rarity of 46 XY DSD, a gynecologist will get to see only a few of these cases in whole of his or her career. A basic understanding of these conditions will help in diagnosis. Long term care of 46 XY women is best provided by a multidisciplinary team comprising of gynecologist, endocrinologist and clinical psychologist having experience in dealing with these disorders.[13]

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Turner Syndrome: Diagnosis and Management

Rakhi Malhotra[1], Rajesh Khadgawat[2]
[1]Assistant Professor, Department of Endocrinology & Metabolism, Army Hospital (R&R), New Delhi;
[2]Professor, Department of Endocrinology & Metabolism, All India Institute of Medical Sciences, New Delhi

Introduction

Turner syndrome (TS) affects 25–50 per 100,000 females. It is characterized by presence of one intact X chromosome and partial or complete absence of the second X chromosome in association with one or more clinical manifestations. The broad clinical spectrum of TS ranges from a classic phenotype to individuals who have no apparent or minimal observable features; including short stature which is also not ubiquitous. The clinical manifestations may be influenced by karyotypes involved, presence and degree of mosaicism, parental origin of intact X chromosome and epigenetic factors. These patients may be seen by different subspecialties through different stages of life and high clinical index of suspicion may help in the correct diagnosis of these girls early in life for better comprehensive care. Numerous advances have taken place in the care of these patients right from prenatal diagnosis to management through various stages of life.

The karyotype in TS ranges from complete 45, X to forms of mosaicism in which there is a normal (46, XX or 46, XY) cell line or an abnormal second (or third) cell line in a female.

Diagnosis of TS should not be considered in females with one X chromosome and a deletion distal to Xq24 on the other X chromosome, and in women over the age of 50 years with less than 5% 45, X mosaicism.

Karyotype Phenotype Correlation in TS

Compared to patients with a 45, X karyotype:

a) 45,X/46,XX mosaicism is associated with a milder phenotype. They have less prevalent and less severe congenital heart disease and lymphatic abnormalities. Mosaicism varies with tissue type and patient age[1,2].

b) 45,X/46,XX and various other forms of mosaicism are more likely to attain normal puberty and spontaneous pregnancies although they experience frequent early miscarriages[3,4].

c) 45,X/47,XXX mosaicism has a milder phenotype[5].

d) The presence of a Y chromosome detected by standard karyotype or FISH (fluorescent *in situ* hybridization) is associated with an increased risk of gonadoblastoma[6]. Gonadectomy should be considered in these patients.

e) A ring X chromosome may be associated with intellectual disability.[7]

f) Iso-chromosome q may have an increased propensity to develop autoimmune disorders.

Indications for testing

The diagnosis of TS should be a foremost consideration in any female with unexplained growth failure or pubertal delay, with or without:

a) Sequelae of lymphedema: edema of the hands or feet, nuchal fold, neck webbing, low hairline, multiple pigmented nevi and hyperconvex or hypoplastic nails

b) Characteristic facial features: epicanthal folds, downslanting palpebral fissures, low-set ears and micrognathia

c) Left-sided cardiac anomalies:coarctation of the aorta, bicuspid aortic valve and aortic stenosis

d) Markedly elevated follicle-stimulating hormone (FSH)

e) Skeletal anomalies: Cubitus valgus; multiple pigmented nevi; bone anomalies including short fourth metacarpal/ metatarsal, Madelung deformity and scoliosis

f) Chronic OM and conductive or sensorineural hearing loss

g) Learning disabilities, especially affecting visuospatial or nonverbal skills.

Diagnosis of TS

Prenatal diagnosis-

1. **Maternal serum screening:** Abnormal triple or quadruple maternal serum screening (alpha-fetoprotein, human chorionic gonadotropin, inhibin A and unconjugated estriol) may suggest TS, but these tests may be perfectly normal together with normal nuchal fold thickness.

2. **Ultrasonography:** Suspect TS when
   a. Increased nuchal translucency, frank cystic hygroma
   b. Coarctation of aorta, Lt sided cardiac defects
   c. Brachycephaly, renal anomalies, polyhydramnios, oligohydramnios and growth retardation

Ultrasound and maternal serum screening are not diagnostic, and karyotype confirmation of TS is obligatory.

3. **Chorionic villous sampling/amniocentesis:** karyotype by these reflect fibroblast analysis. It should be repeated postnatally in all patients. Uncertainity mainly prevails for mosaics.
4. **Noninvasive prenatal testing (NIPT):** Insufficient evidence to recommend NIPT for TS. Done by SNP (single-nucleotide polymorphism) arrays or analysis of cell-free fetal DNA (cf-DNA) in maternal blood.
5. **Preimplantation genetic screening (PGS):** Is being used with increased frequency in IVF programs as a method of embryo selection.

Post natal diagnosis

1. All individuals with suspected TS should have a standard 20-cell karyotype as recommended by the American College of Medical Genetics[8,9].
2. If mosaicism is strongly suspected, additional metaphases may be counted or FISH studies performed[10].
3. A second tissue, such as skin fibroblasts, buccal mucosa cells or urine for bladder epithelial cells may be examined if there is a strong clinical suspicion of TS despite a normal blood karyotype or low-level mosaicism.
4. Role of chromosomal microarray analysis in diagnosis of TS is supplementary.
5. Newborn screening with karyotype is not routinely recommended for TS and the clinical practice guidelines recommend that newborn screening should be considered after additional improvements in methodology.

Management of TS

Growth and Puberty

1. Growth hormone therapy should be initiated early(around 4–6 years of age, and preferably before 12–13 years)
2. Recommended GH dose: 45-50 µg/kg/day increasing to 68 µg/kg/day if adult height potential is severely compromised.
3. Growth velocity should be monitored at least every 4-6 months during the first year of treatment and at least every 6 months thereafter.
4. IGF-1 should be measured annually on treatment with GH. IGF-1 should ideally be no greater than 2 SDS above the mean for age. Dose of GH should be reduced if IGF-1 value is above 3 SDS.
5. Therapy should be continued till BA $\geq$ 14 years or HV <2cm/year.
6. Concomitant treatment with oxandrolone may be given from the age of 10 years or older at 0.03 mg/kg/day and maintained below 0.05 mg/kg/day, if the diagnosis of TSis delayed and adult height outcome with standard dose of GH is likely to be unsatisfactory alone.
7. Very-low-dose estrogen supplementation in the prepubertal years to further promote growth is not recommended.

Puberty induction and sex hormone replacement

Turner syndrome is usually accompanied by hypergonadotropic-hypogonadism and primary or secondary amenorrhea due to gonadal dysgenesis. The most patients with TS will therefore need HRT for induction of puberty and for maintaining female secondary sex characteristics, attaining peak bone mass and normalizing uterine growth.

Timing of puberty induction

Estrogen replacement should start between 11 and 12 years of age, increasing to adult dosing over 2–3 years. It is usually administered by systemic route however transdermal route has shown many advantages but very infrequently used.

Estrogen preparations available in the market

- Ethinylestradiol (EE) – commonly used, cost effective, can be continued as OCPs after addition of progesterone
- Estradiol valerate or 17β- estradiol – is naturally occurring estrogen, which is partly metabolized in liver to form E3/E1 hence oral bioavailability is low. Replacement with Estradiol valerate is more physiological, but costly.
- Conjugated equine estrogen (CEE) – used in past extensively for induction of puberty in hypogonadism but now a days, contraindicated for puberty induction. CEE not only contain estrogen but also contain estrone (>50%), equilin/equilenin and >100 forms of minor estrogens. It also contains multiple minor androgens and progestogens. Equilin/Equalenin are foreign substances to the human body and not known to have estrogenic effect or side effects.
- Transdermal Estrogen (TDE) patch – are more popular for adult HRT rather than puberty induction. TDE directly absorbed into systemic circulation, there by avoid hepatic first-pass metabolism and shown to be potentially lower thrombogenic and more neutral effect on lipids however, limited experience is one of the major restriction. TDE has also shown to have better bone mineral accrual and uterine development. Another important limitation is huge individual variability in drug absorption

thereby producing about tenfold difference. Patches strength available are 25, 50, 75 and 100 µg/day dose delivery (as they are used for HRT). These patches are to be cut into multiple pieces and then one piece is to be used by applying over non-wrinkle skin twice a week, over thigh/buttock area.

Equivalent doses of estrogens

1 mg 17β- estradiol = 10 μg ethinyl estradiol = 0.625 mg CEE = 50 μg Transdermal estradiol

Principle of induction

It is similar to normal pubertal development with slow gradual rise in estrogen level over long time, without interference from progesterone. From initiation to full adult dose replacement should be completed in 2-4 yrs. The starting dose is usually 1/4 to 1/8 of adult replacement dose which is gradually increased over next few years.

Fast induction of puberty with higher doses of estrogen may result in poor breast and uterus development, and also poor bone mass build-up.

Doses to be used for induction are given in table 1, 2 and 3.

Table 1. Induction using Ethinylestradiol (EE)

Months	Dose per day	Tablet to be given
First 6 months	2.5 μg per day	Half tablet every alternate day or One fourth of tablet every day or One tablet twice a week
6-12 months	2.5 μg per day	Half tablet every alternate day or One fourth of tablet every day or One tablet twice a week
12-24 months	5 μg per day	Half tablet daily or One tablet every alternate day
24 months to till breakthrough bleeding occurs	10 μg per day	One tablet every day

Table 2. Induction using Estradiol valerate (17β- estradiol)

Months	Dose per day	Tablet to be given
First 6 months	5 μg per Kg wt per day	Body weight – 45 kgs; Half tablet every alternate day or One fourth of tablet every day
6-12 months	5 μg per Kg wt per day	Body weight – 45 kgs; Half tablet every alternate day or One fourth of tablet every day
12-24 months	*10* μg per Kg wt per day	Body weight – 45 kgs; Half tablet daily or One tablet every alternate day
24 months to till breakthrough bleeding occurs	20 μg per day	One tablet every day

Table 3. Induction using Estrogen patch

Months	Dose per day	Tablet to be given
First 6 months	25 μg twice a week	Half a patch twice a week
6-12 months	25 μg twice a week	Half a patch twice a week
12-24 months	50 μg twice a week	one patch twice a week
24 months to till breakthrough bleeding occurs	100 μg per day	100 μg patch twice a week

Why not to use OCP for induction?

OCPs are to be best avoided for induction of puberty as they contain very high estrogen doses which can lead to faster epiphyseal closure resulting in short stature and at the same time, can lead to very fast progression of puberty. Progestin, present in OCP would interfere with optimal breast and uterine development, especially very poor and mis-shaped breast (tubular) development.

Precautions during induction

- Any subject developing feature of one of the following, therapy should be interrupted temporarily and investigated further.
- Hepatitis or jaundice or significant liver dysfunction.
- Thrombophlebitis or thromboembolic disorders.
- Lump in breast or breast abscess.
- EE – all subjects receiving EE, BP should be regularly checked as use of EE can lead to newly developed hypertension in some patients.

Additional of Progesterone

Once breakthrough bleeding occurs, it is necessary to add progesterone to prevent endometrial hyperplasia occurs. It usually occurs after 2 years of estrogen treatment however, it may occur early laso. Medroxy Progesterone Acetate (MPA), 5 mg/day for 10 days or 10 mg/day for 7 days is preferred approach. Micronized oral progesterone can also be used in doses of 200–300 mg/day for 10 days. Common side effects of MPA are fluid retention, insomnia, headache, nausea, and breast tenderness.

Can we switch to OCPs after breakthrough bleed?

Many subjects continue sequential E + P however, however use of OCPs (EE 20-50 ug + LNG 0.1-0.3 mg) is the easiest way to continue. If OCPs are used, lowest possible dose of estrogen should be used. Transdermal patch of OCPs are in developmental stage yet.

Fertility, Assisted reproductive technologies and Pregnancy

1. All females with TS should be counseled that their ability to conceive spontaneously decrease rapidly with age. Spontaneous pregnancies occur in 4.8–

7.6% of women with TS[3,4], but the frequency of miscarriages after spontaneous pregnancy is reported to be high: 30.8–45.1%.[3,4]

2. Young mosaic TS women with persistent ovarian function should be counseled about oocyte cryopreservation after controlled ovarian hyperstimulationas a possible fertility preservation option.
3. For most patients with TS,oocyte donation (OD) is the only way to achieve a viable pregnancy.
4. Women with TS who conceive with OD are at high risk for obstetrical complications like pre-eclampsia and higher rates of cesarean section.
5. Intensive cardiac screening is recommended before pregnancy. Women with a history of aortic dilatation (AoD) should be advised against pregnancy. ART or spontaneous conception should be avoided in case of an ascending ASI (Aortic size index) of >2.5 cm/m^2.
6. Women with TS with an ascending ASI >2.0 cm/m^2 or any risk factor (hypertension, bicuspid aortic valve, coarctation, previous AoD or surgery) should be monitored frequently, including TTE at 4- to 8-week intervals during pregnancy and during the first 6 months postpartum
7. Blood pressure control should be strict (135/85 mmHg) in all pregnant women with TS.

Congenital heart disease in TS

1. Congenital heart disease occurs in 23-50% individuals with TS[12,13]. Left-sided obstructive lesions are most common, with a baseline prevalence of 15–30% for bicuspid aortic valve and 7–18% for coarctation[14,15].
2. Neck webbing and an increased anterior–posterior thoracic diameter have been shown to be strong predictors of arterial and venous anomalies in TS[15].
3. Additional less frequently occurring anomalies include hypoplastic left heart syndrome, mitral valve anomalies, interrupted inferior vena cava with azygous continuation, cardiac dextroposition, ventricular septal defect, atrioventricularseptal defect, pulmonary valve abnormalities, coronary artery anomalies[16,17] and patent ductusarteriosus[18].

Cardiac Monitoring in Turner Syndrome

1. Transthoracic Echocardiography (TTE) should be done for all individuals with TS at the time of diagnosis.
2. CMR study for the heart should be performed in all patients as soon as it is feasible without needing GA
3. Due to the high prevalence of undiagnosed abnormalities such as elongation of the transverse aortic arch, aortic coarctation and partial anomalous pulmonary venous return in TS, CMR as a screening and surveillance tool has gained utility (19,20). CMR is also more sensitive than TTE to changes in aortic size, particularly beyond the aortic root.
4. In the absence of a bicuspid aortic valve or other significant disease at the initial screening, TTE or CMR surveillance studies should be performed every 5 years in children, every 10 years in adults, or prior to anticipated pregnancy.
5. Diagnosis of a bicuspid aortic valve or a left-sided obstructive lesion in a female fetus or child should prompt a genetic evaluation for TS.
6. A resting electrocardiogram (ECG) with QTc measurement should be done in every individual with TS at the time of diagnosis.
7. In individuals without structural heart disease, annual assessment of blood pressure should be performed and medical treatment should be considered if hypertension is present.
8. A resting electrocardiogram (ECG) with QTc measurement should be done in every individual with TS at the time of diagnosis. Caution with the use of QT-prolonging drugs may be warranted in this population.
9. 24-h Holter monitoring and exercise testing be considered for risk estimation in women with TS with QTc interval prolongation (QTc>460 ms).

Hypertension

1. Individuals with TS have systemic hypertension in several studies with frequency as high as 20–40% in childhood and in as many as 60% of adults[21,22]
2. In individuals without structural heart disease, annual assessment of blood pressure should be performed. Antihypertensive drugs should include β blocker, ARB or both to reduce the risk for AoD in women with TS.
3. Left ventricular hypertrophy has been identified in TS, even in those who are normotensive[23]. This could be an end-organ effect of hypertension that is masked during resting blood pressure assessment or is related to loss of diurnal variation (lack of night-time dipping).
4. Ambulatory blood pressure monitoring (ABPM) is considered useful in demonstrating abnormal diurnal variation in blood pressure values in women with TS[24].

Otolaryngology problems

1. Hearing impairment in TS is multifactorial in etiology. Anomalies of the external ear have been described in up to 34% of patients and include

low-set and abnormally protruding pinnae, cupped auricles and narrowing of the external auditory canal[25]. In addition, hearing abnormalities are likely related to abnormal craniofacial morphology such as delayed development of the cranial skeleton, a downward slope of the external auditory canal and abnormal orientation of the Eustachian tubes.

2. A formal audiometric evaluation every 5 years regardless of initial age at diagnosis is recommended to assure early and adequate technical and other rehabilitative measures.
3. Conductive hearing loss (CHL) is common due to middle-ear effusion, frequent Otitis media and tympanic membrane pathology.
4. Sensorineural hearing loss (SNHL) is the prevailing hearing impairment in females with TS and its exact pathology is not clearly understood.

Autoimmunity

1. Individuals with TS have an increased rate of development of several autoimmune disorders, including thyroid disease (thyroiditis, hyperthyroidism and hypothyroidism), celiac disease and, to a lesser degree, type 1 diabetes mellitus, alopecia areata, jenile rheumatoid arthritis, uveitis and inflammatory bowel disease (IBD) [26].

Obesity, Diabetes and Lipid disorders

2. Individuals with TS have a higher BMI, higher percent body fat, larger waist circumference and lower percent lean body mass than age- and BMI-matched peers[27].
3. Annual lifelong measurement of HbA1c with or without fasting plasma glucose starting at the age of 10 years is recommended as the risk of both type 1 and type 2 diabetes mellitus is about 10-fold and 4-fold increased in patients with TS across all ages in epidemiological studies[28].
4. Lipid profile should be performed in individuals who have at least one risk factor for cardiovascular disease starting at age 18 years. An elevated cholesterol concentration should first prompt an assessment for secondary causes, e.g., hypothyroidism, and treatment could follow the recommendations for the general population.

Dental

1. Females with TS may present with variations in dental eruption, changes in crown and root morphology, and an increased risk for root absorption with subsequent tooth loss especially during orthodontic treatment.
2. Females with 45, X or with 45, X/46isoXq mosaicism have more severe oral and dental anomalies, while those with a 45,X/46,XX karyotype tend to have abnormalities in line with the general population[29].

Opthalmology

1. A comprehensive ophthalmological examination between 12 and 18 months of age or at the time of diagnosis is recommended.
2. Refractive errors are present in about 40% of girls and women with TS. Strabismus and amblyopia each occur in roughly one-third of females with TS.Ptosis (16%), epicanthal folds, hypertelorism and downward-slanting palpebral fissures are also common.

Orthopaedics

An increased risk of kyphosis, vertebral wedging and scoliosis occurs in patients with TS.A clinical evaluation for scoliosis every 6 months during GH therapy or otherwise annually until growth is completed is recommended.

Gastrointestinal and liver disease

1. Screening for celiac disease should be done by measurement of transglutaminase antibodies beginning at 2–3 years of age at a frequency of every 2 years throughout childhood
2. Liver function tests (including AST, ALT, GGT and alkaline phosphatase) should be monitored yearly throughout the lifespan starting at age 10 years.
3. The prevalence of IBD in patients with TS is increased (0.15–3%) [30]. Any TS patient who has abdominal pain, unexplained weight loss, diarrhea and/ or intestinal bleeding should be evaluated for IBD.

Renal disease

1. A renal ultrasound is recommended at the time of diagnosis.The spectrum of renal anomalies in patients with TS is broad and affects 24–42%[31].
2. Anomalies described include horseshoe (11%) and partially or totally duplicated (5–10%), absent (2–3%), multicystic (<1%) or ectopic (<1%) kidneys.
3. Collecting duct and ureteral anomalies, both congenital and acquired, are also common, and include duplications, obstructions and hydronephrosis (5–15%).

Psychological

Individuals with TS are at an increased risk of social isolation, anxiety, and obsessive behavior. They have higher levels of shyness and social anxiety, and reduced self-esteem.

Suggested Reading

Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting.

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Pre-menstrual Syndrome

Mala Srivastava
Senior Consultant & Robotic Surgeon, Institute of Obstetrics and Gynaecology, Sir Ganga Ram Hospital, New Delhi

Definition

Pre-menstrual Syndrome includes a spectrum of psychological symptoms such as depression, anxiety, irritability, loss of confidence and mood swings. There are also physical symptoms which includes bloatedness and mastalgia. It is the timing, rather than the types of symptoms, and the degree of impact on daily activity that supports a diagnosis of PMS. In order to differentiate physiological menstrual symptoms from PMS, it must be demonstrated that symptoms cause significant impairment during the luteal phase of each menstrual cycle.

Classification of PMS (International Society for Premenstrual Disorders Consensus)

The core premenstrual disorders (PMDs) are the most common type of PMS. The symptoms of the woman must be severe enough to affect her daily activity or interfere with her work, school performance or interpersonal relationships. The symptoms of core PMDs are nonspecific and recur in ovulatory cycles. They must be present during the luteal phase and abate as menstruation begins, which is then followed by a symptom-free week.

There are also PMDs that do not meet the criteria for core PMDs. These are called 'variant' PMDs and fall into four subtypes.

1. 'Premenstrual exacerbation of an underlying disorder', such as diabetes, depression, epilepsy, asthma and migraine. These patients will experience symptoms relevant to their disorder throughout the menstrual cycle.
2. 'Non-ovulatory PMDs' occur in the presence of ovarian activity without ovulation.
3. 'Progestogen-induced PMDs' are caused by exogenous progestogens present in hormone replacement therapy (HRT) and the combined oral contraceptive (COC) pill.
4. 'PMDs with absent menstruation' include women who still have a functioning ovarian cycle, but for reasons such as hysterectomy, endometrial ablation or the levonorgestrel-releasing intrauterine system (LNG-IUS) they do not menstruate

Prevalence

Approximately four in ten women (40%) experience symptoms of PMS and of these 5–8% suffer from severe PMS [1].

Aetiology

Although the aetiology remains uncertain, it revolves around the ovarian hormone cycle, which is reinforced by the absence of PMS prior to puberty, during pregnancy and after the menopause. There are two theories regarding PMS and appear interlinked. The first suggests that some women are 'sensitive' to progesterone and progestogens. The second theory implicates the neurotransmitters serotonin and c-aminobutyric acid (GABA). Serotonin receptors are responsive to estrogen and progesterone, and selective serotonin reuptake inhibitors (SSRIs) are proven to reduce PMS symptoms.

Diagnosis

When clinically reviewing women for PMS, symptoms should be recorded prospectively, over two cycles using a symptom diary, as retrospective recall of symptoms may be unreliable.

There are many patient-rated questionnaires available. However, the Daily Record of Severity of Problems (DRSP) remains the most widely used and is simple for patients to use [2]. Before any form of treatment is initiated, symptom diaries should be completed over at least two consecutive menstrual cycles.

Symptom diaries can sometimes be confusing and inconclusive: this is most likely to occur in those patients with variant PMDs. GnRH analogues, can be useful in separating those with and those without PMS by inhibiting cyclical ovarian function. These should be used for 3 months to establish a definitive diagnosis.

Women with severe PMS benefits by being managed by a multidisciplinary team consisting of a general practitioner, a general gynaecologist or a gynaecologist with a special interest in PMS, a mental health professional (psychiatrist, clinical psychologist or counsellor) and a dietician. A multidisciplinary team can offer women an individualised management plan utilising a range of treatments, such as cognitive behavioural therapy (CBT) and lifestyle interventions.

Management

Although there is limited evidence to support the use of complementary therapies, some women with PMS may benefit. This is particularly important for women in whom hormonal therapy is contraindicated. Unsaturated fatty acids, contained evening primrose oil, have been shown in randomised trial to improve menstrual symptoms compared with placebo at both 1 g/day and 2 g/day dosages[3].

Whelan et al. conducted a systematic review of 29 randomised controlled trials (RCTs). Two of these studies (n = 499) revealed consistent evidence for calcium in alleviating both physical and psychological symptoms of PMS. The evidence for vitamin B6 was contradictory in this review and therefore advice could not be given for vitamin B6 Therapy[4].

The RCTs including St John's Wort (Hypericum perforatum) show conflicting results [5]. St John's Wort interacts with other medications. So, it should not be used concurrently with SSRIs and can render low dose COCs ineffective.

The Cognitive Behavioural Therapy should be considered routinely as a treatment option. Hunter et al. [6] conducted a randomised trial comparing fluoxetine, CBT and the combination of fluoxetine and CBT for the treatment of PMDD. Fluoxetine showed quicker improvements; however at follow-up CBT was associated with better maintenance of treatment effects compared with fluoxetine.

CBT also cause a significant reduction in depression, anxiety and behavioural problems. If CBT proves successful to a patient it would avoid pharmacotherapy and potential adverse effects.

The drospirenone-containing COCs may represent effective treatment for PMS and should be considered as a first-line pharmaceutical intervention.

There is an emerging data to suggest use of the contraceptive pill continuously rather than cyclically. The results concluded that mood, headache and pelvic pain scores improved when compared with a 21/7-day regimen. There was a high level of satisfaction, with most women continuing on this regimen 6 months [7].

Percutaneous estradiol combined with cyclical progestogens has been shown to be effective for the management of physical and psychological symptoms of severe PMS.

But together with oestradiol the alternative barrier or intrauterine methods of contraception should be used.

Use of continuous estradiol necessitates the addition of cyclical progesterone or progestogens

(10–12 days/cycle) to avoid endometrial hyperplasia in women who have a uterus. Intrauterine administration of progestogen has the potential to avoid systemic absorption and hence minimise progestogenic effects. The LNG-IUS 52 mg as progestogen replacement can maximise efficacy by minimising PMS-like adverse effects [8].

Micronised oral progesterone (100 or 200 mg) has fewer androgenic and unwanted adverse effects compared with other progestogens[9]. Micronised progesterone can also be administered vaginally, which may be better tolerated by avoiding first-pass hepatic metabolism [10].

When treating women with PMS using estradiol, percutaneous patches and cyclical progestogens women should be informed that there are insufficient data to advise on the long-term effects on breast and endometrial tissue.

The cycle suppression may be achieved using danazol, an androgenic steroid. A randomised, double-blind, cross-over study compared three successive cycles of danazol at a dose of 200 mg twice daily with three cycles of placebo[11]. From this study, the authors demonstrated that danazol at a dose of 200 mg twice daily was superior to placebo for the relief of severe PMS during the premenstrual period. Danazol therapy have some adverse effects which includes symptoms of acne, weight gain, hirsutism and deepening of the voice.

One study of danazol given in the luteal phase demonstrated improvement in breast symptoms only, but with minimal adverse effects. Women treated with danazol for PMS should be advised to use contraception during treatment due to its potential virilising effect on female fetuses.

GnRH analogues are highly effective in treating severe PMS. But GnRH analogues should be reserved for women with the most severe symptoms and not recommended routinely.

GnRH analogues suppress ovarian steroid production and therefore cause a drastic improvement or complete cessation of symptoms in patients with core PMDs, but their effects on bone mineral density (BMD) mean that they should only be considered for severe cases [12].

If women is treated with GnRH analogues for more than 6 months, add-back hormone therapy should be used.

For add-back hormone therapy, continuous combined HRT or tibolone is recommended. Continuous combined therapy or tibolone is preferable to sequential combined therapy in order to minimise the risk of reappearance of PMS-like progestogenic adverse effects.

Women should be provided with general advice

regarding the effects of exercise, diet and smoking on BMD.

Women on long-term treatment should have measurement of BMD (ideally by dual-energy

X-ray absorptiometry [DEXA]) every year. Treatment should be stopped if bone density declines significantly.

As symptoms return with the onset of ovarian function, therapy may (rarely) have to be continued indefinitely; GnRH alone is precluded by significant trabecular bone loss, which can occur with only 6 months of treatment. It should be noted that GnRH analogues are only licensed for use for 6 months when used alone and are not licensed to treat PMS [13].

Role of Progesterone and Progestogen Preparation

There is evidence that treating PMS with progesterone or progestogens is not appropriate.

Its role should be confined to opposing the action of estrogen therapy on the endometrium.

Non-Hormonal Medical Management of PMS

SSRIs should be considered one of the first-line pharmaceutical management options in severe PMS. For treatment either luteal or continuous dosing with SSRIs can be done.

The exact mode of action of SSRIs is unknown in PMS; however, both estrogen and progesterone have the ability to regulate the number of serotonin receptors [14].

A Cochrane review analysed data from 31 RCTs comparing SSRIs with placebo. SSRIs compared included fluoxetine, paroxetine, sertraline, escitalopram and citalopram and this showed that symptoms improved when compared with placebo[15].

When evaluating continuous dosing versus luteal dosing there was no significant difference between the SSRI regimens. SSRIs appear to be effective for both physical and psychological symptoms.

SSRIs should be discontinued gradually to avoid withdrawal symptoms, if given on a continuous basis. Gastrointestinal disturbances, headache, anxiety, dizziness, paraesthesia, sleep disturbances, fatigue, influenza-like symptoms and sweating are the most common features of abrupt withdrawal of an SSRI or marked reduction of the dose; the dose should be tapered over a few weeks to avoid these effects. Women with PMS treated with SSRIs should be warned of the possible adverse effects such as nausea, insomnia, somnolence, fatigue and reduction in libido. All of these adverse effects are dose-dependent.

Women should be provided with pre-pregnancy counselling at every opportunity. They should be informed that PMS symptoms will abate during pregnancy and SSRIs should therefore be discontinued prior to and during pregnancy. Women with PMS who become pregnant while taking an SSRI/SNRI should be aware of the possible, although unproven, association with congenital malformations.

Spironolactone can be used in women with PMS to treat physical symptoms. Women taking spironolactone showed improvement in mood and somatic symptoms when compared with placebo[16]. The benefit for physical symptoms, in particular reduced weight gain.

In women with severe PMS, hysterectomy and bilateral oophorectomy has been shown to be of benefit. The hysterectomy and bilateral oophorectomy can be considered when medical management has failed, long-term GnRH analogue treatment is required or other gynaecological conditions indicate surgery.

Hysterectomy and bilateral oophorectomy is a permanent form of ovulation suppression, as this removes the ovarian cycle completely; it also removes the endometrium, allowing the use of estrogen replacement without the need for progestogen.

Severe PMS is in most cases treated successfully with medical management, but hysterectomy with bilateral oophorectomy can be justified in women in whom medical management has proven unsuccessful, where long-term GnRH analogue treatment would be required, or if gynaecological comorbidities indicate hysterectomy.

Women being surgically treated for PMS should be advised to use HRT, particularly if they are younger than 45 years of age.

Following hysterectomy, estrogen-only replacement can be used. Consideration should also be given to replacing testosterone, as the ovaries are a major production source (50%) and deficiency could result in distressing low libido.

In women with severe PMS, endometrial ablation and hysterectomy with conservation of the ovaries are not recommended.

Bilateral oophorectomy alone (without removal of the uterus) will necessitate the use of a progestogen as part of any subsequent HRT regimen and this carries a risk of reintroduction of PMS-like symptoms (progestogen-induced PMD). There have been no published studies of bilateral oophorectomy with uterine conservation in PMS. If such a strategy is employed then women should be counselled regarding the lack of research evidence and thus potential return of symptoms.

Conservation of the ovaries will lead to persistence of PMS (ISPMD classification: PMDs with absent menstruation)[17].

Summary of treatment of PMS

First line Exercise, cognitive behavioural therapy, vitamin B6 Combined new generation pill (cyclically or continuously) Continuous or luteal phase (day 15–28) low dose SSRIs, e.g. citalopram/escitalopram 10 mg

↓

Second line Estradiol patches (100 micrograms) + micronised progesterone (100 mg or 200 mg [day 17–28], orally *or* vaginally) or LNG-IUS 52 mg Higher dose SSRIs continuously or luteal phase, e.g. citalopram/escitalopram 20–40 mg

↓

Third line GnRH analogues + add-back HRT (continuous combined estrogen + progesterone [e.g. 50–100 micrograms estradiol patches *or* 2–4 doses of estradiol gel combined with micronised progesterone 100 mg/day] or tibolone 2.5 mg)

↓

Fourth line Surgical treatment ± HRT

Conclusion

Pre-menstrual Syndrome is a unique gynaecological condition. The diagnosis should be accurate so that an appropriate management option can be chosen.

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Calendar of Monthly Clinical Meetings 2019-20

Months	Name of the Institute
17th January, 2020	Dr RML Hospital
28th February, 2020	UCMS & GTB Hospital
27th March, 2020	LHMC
24th April, 2020	Apollo Hospital

Hyperprolactinaemia

Tarang Preet Kaur[1], Vidushi Kulshrestha[2]
[1]Senior Resident, [2]Associate Professor, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi

Definition

Serum prolactin (PRL) levels more than 25 ng/ml (cut-off is 20 ng/ml in some laboratories) when sample is withdrawn under ideal conditions.

Etiology of Hyperprolactinemia

Hyperprolactinemia is caused by hypersecretion of prolactin by lactotroph cells of pituitary gland. Some of these causes are physiologic or drug induced and others are due to diseases of pituitary or stalk damage.

Pituitary / Hypothalamic- Pituitary Stalk Damage:

- Tumours- Pituitary: Prolactinoma (prolactin secreting adenoma or lactotroph adenomas), Plurihormonal adenoma
  Supra-sellar pituitary mass extension
  Hypothalamic tumours: craniopharyngioma, meningioma
- Surgery, trauma
- Infections: Hypophysitis, Granulomas
- Acromegaly
- Macroprolactinemia*
- Rathke's cyst
- Irradiation

Physiological causes: Pregnancy, Lactation, Exercise, Stress

Drug Induced: Dopamine inhibitors, Antihistamines, Antipsychotics, Opiates and opiate antagonists, Anesthetics, Anticonvulsants, antidepressants, Cholinergic agonist, OCPs

Chest wall trauma, surgery, burns or herpes zoster: due to a neural mechanism similar to suckling

Chronic renal or liver failure: due to decreased prolactin clearance

Pseudocyesis

**Adenomas measuring <10 mm are termed microadenoma, and ≥ 10 mm are termed macroadenoma. Pituitary adenomas secreting prolactin are known as prolactinomas.*

Clinical Presentation of Hyperprolactinemia

The clinical manifestations of hyperprolactinemia are relatively few and usually easy to recognize. Once the presence of prolactin excess is identified, further evaluation to establish the underlying cause is usually straightforward.

A serum prolactin concentration greater than 100 ng/mL (100 mcg/L SI units) is typically associated with overt hypogonadism, subnormal estradiol secretion, and its consequences, including amenorrhea, hot flashes, and vaginal dryness.

- Galactorrhea - 80% cases (30% hyperprolactinemic women may present only with galactorrhea)
- Ovulatory and menstrual dysfunction
  - In mild hyperprolactinemia (PRL levels 20-50 ng/ml) : Short luteal phase as milder degree causes only insufficient progesterone secretion
  - In moderate cases (PRL levels 50-100 ng/ml): Oligomenorrhea/ amenorrhea
  - In severe cases (PRL levels > 100 ng/ml) : Overt hypogonadism with hypoestrogenism
- Infertility: Mild hyperprolactinemia can cause infertility even when there is no abnormality of the menstrual cycle
- Hot flashes and vaginal dryness due to hypogonadism.
- Hirsutism
- Sexual dysfunction, decreased libido
- Osteoporosis: Women with amenorrhea secondary to hyperprolactinemia have a lower spine and forearm bone mineral density
- Neurological manifestations - These are common with macroadenomas or giant adenomas (>5 cm), because of possible compression of optic chiasma. Neurological symptoms include headaches, visual impairment ranging from quadrantanopia to classical bitemporal hemianopia or scotomas.
- Blindness owing to an expanding prolactinoma may occur in pituitary apoplexy.
- **Ahmuda-Del-Castillo syndrome** - Galactorrhea & amenorrhea together, seen in 60% of patients
- **Chiari Frommel Syndrome**- Refers to extended postpartum galactorrhea & amenorrhea
- **Forbes Albright Syndrome**- refers to galactorrhea & amenorrhea syndrome associated with pituitary tumor
- **Postmenopausal women** —
- Postmenopausal women are already hypogonadal and hypoestrogenic, hence usually remain asymptomatic in hyperprolactinemia and very rarely present with galactorrhea is rare.
- Hyperprolactinemia is detected only when pressure symptoms appear due to large adenoma size or as an incidental finding on MRI done for some other indication.

Pathophysiology

- Prolactin secretion is enhanced by estrogen, throtropin releasing hormone (TRH) and inhibited by dopamine.
- Hyperprolactinaemia interrupts the pulsatile GnRH secretion → inhibits LH and FSH release → directly impairs gonadal steroidogenesis → leading to primary or secondary amenorrhoea.
- Chronic hyperprolactinaemia → induces hypogonadism → reduces spinal bone mineral density (BMD). BMD increases after prolactin normalization but does not always return to normal.
- Pressure symptoms of very large pituitary

tumours → compression of other pituitary cells or hypothalamic–pituitary stalk → leading to panhypopituitarism.

Evaluation of Hyperprolactinemia

History — Rule out pregnancy and intake of medications that can cause hyperprolactinemia. Ask about headache, visual symptoms, symptoms of hypothyroidism, and a history of renal disease.

Physical examination — Test for chiasmal syndrome (eg, bitemporal field loss) and look for chest wall injury and signs of hypothyroidism or hypogonadism.

Investigation in Suspected Hyperprolactinemia

Serum PRL levels

- Normal range in females: 5- 25 ng/ml (20 ng/ml in some laboratories)
- PRL Levels are
  - Highest between 5-7 AM
  - Lowest in mid-morning (about 2 hours after patient wakes up)
- Physiological increase is seen after meals, excessive exercise, chest wall surgery or trauma, breast stimulation, venipuncture and 1-2 hours postictal.

Measurements of serum PRL

- A single measurement above the upper limit of normal confirms the diagnosis (as long as the serum sample was obtained without excessive venepuncture stress).
- Food has only a small effect on serum PRL concentrations; therefore, fasting is usually not necessary. However, a repeat fasting sample should be taken if initial serum PRL is 21- 40 ng/mL before labelling hyperprolactinemia because meals may stimulate prolactin secretion slightly.
- To avoid the effect of pulsatile secretion, 2-3 samples are taken, separated by at least 15-20 minutes (pooled sample).

Diagnostic Pitfalls:

- **Macroprolactin:** Macroprolactin causes hyperprolactinemia through decreased prolactin clearance.It is native prolactin that is bound to immunoglobulin G (IgG) and is 150 to 170 kDa in size, compared with 23 kDa for monomeric prolactin. Macroprolactin has reduced bioactivity and is present in significant amounts in up to 20%, resulting in pseudo-hyperprolactinaemia and potential misdiagnosis. Misdiagnosis can be avoided by asking the laboratory to pre-treat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin in the supernatant. Rule out the presence of macroprolactin in patients with moderately elevated PRL levels (20–200 ng/mL) and less typical symptoms.
- **Hook effect:** Caution should be exercised in interpreting serum prolactin concentrations between 20 and 200 ng/mL (20 to 200 mcg/L SI units) in the presence of a macroadenoma because of falsely low values due to the "hook effect". It occurs when serum prolactin levels are very high (5000 ng/ml). Increased amount causes antibody saturation in the immunoradiometric assay, leading to falsely low levels. The artifact can be avoided by repeating the assay using a 1:100 dilution of serum.

Pituitary Imaging

- Dynamic Contrast MRI (Gadolinium-enhanced) – look for a mass lesion in hypothalamic pituitary area, extent of tumour, suprasellar extension, and compression of optic chiasma or invasion of the cavernous sinus.
- MRI for a patient with any degree of renal impairment should be done without gadolinium.

Additional evaluation:

- LH, FSH when a gonadotroph adenoma is suspected.
- T4, TSH when a thyrotroph adenoma is suspected.
- Peripheral visual field examination for patients with macroadenomas abutting the optic chiasm.

Management of Hyperprolactinemia

Expectant Management

- Can be done in premenopausal women with normal menstrual cycles and postmenopausal women with tolerable galactorrhea who have idiopathic hyperprolactinemia or macroprolactinoma.
- Regular follow up with serum prolactin levels to detect potential enlarging tumors. Once menopause is attained, these levels may normalize.

Medical Management

All patients with macroadenomas and most patients with microprolactinoma

Indications of treatment:

- Pituitary tumor with neurological defects (visual field defects)
- Features of hypogonadism or hyperprolactemia
  - Galactorrhea
  - Infertility
  - Preventing bone loss due to hypogonadism in long standing hyperprolactinemia
  - Altered pubertal development
- Even in mild hyperprolactinemia and normal cycles in women trying to conceive as there may be subtle luteal phase dysfunction

Management of drug induced hyperprolactinemia:
Withdraw the drug or switch to an alternative drug if possible

Idiopathic hyperprolactinemia —

- Patients have raised serum prolactin concentration, usually between 20 and 100 ng/mL but no cause could be found.
- Many of these patients may have microadenomas not visible on imaging studies.
- Serum prolactin should be measured yearly.

Dopamine Agonists (DA) are the mainstay of medical management and are effective in normalizing prolactin levels and reducing volume of pituitary tumor.

Drug	Type of dopamine agonist	Dosage	Remarks
Cabergoline	Ergot derivative Selective type 2 dopamine receptor agonist	0.25-0.5 mg once or twice weekly	- Drug of choice - Longer acting - Better compliance (less nausea, orthostatic hypotension) - Superior in reducing prolactin secretion (95% cases) - Greater reduction of tumor volume (90% cases) - Increased restoration of hypogonadism - Works even in bromocriptine resistant cases (80% respond)
Bromocriptine	Ergot derivative Non-selective dopamine receptor agonist	0.625-1.25 mg HS is starting dose. Increased by 1.25 mg per day upto total dose of 5 mg twice daily.	- Restores ovulation in 80-90% cases - Reduces prolactinoma size in 70 % of cases - Less expensive
Quinagolide	Non-ergot derivative	0.075 mg once a day is the starting dose. Maximum dose is 0.9 mg per day	- Equivalent efficacy to cabergoline - Available in some countries
Pergolide	Non-ergot derivative	0.1-0.2 mg/day	- Withdrawn from market due to its association with valvular heart disease at high doses (>3mg/day) used in parkinsonism

Follow-up in patients on medical treatment

- Prolactin levels start decreasing in 2-3 weeks of treatment initiation.
- Tumor size reduces by 6 weeks.
- Menstruation, ovulation and fertility returns after normalization of prolactin levels.
- Serum prolactin levels are repeated at 1-3 monthly intervals and MRI at yearly interval.
- After one year of treatment, dose of dopamine agonist can be reduced. If serum prolactin levels remain normal for 2-3 years and MRI doesn't show any tumor mass, then drug can be stopped.
- Follow-up then includes every 3 monthly serum prolactin levels for first year and then annually. MRI of the brain is done if prolactin levels increase above normal.
- Hyperprolactinemia may recur in 26-65 % cases of macroprolactinoma within a year after treatment withdrawal.

Resistant prolactinomas:

When there is inadequate response to dopamine agonist. Treatment options for such cases are as follows:

- Achieve the maximally tolerated dose
- Change to different dopamine agonist
- Surgery or radiotherapy

Surgical Management

Indications:

- 10 % of patients who donot respond to dopamine agonist
- Intolerance to dopamine agonist
- Visual field defects donot improve
- Apoplexy with neurological signs in macroadenomas
- Nonfunctional tumors
- Patient preference
- If there is suprasellar extension of the tumor that has not regressed with medical treatment and pregnancy is desired

Surgical procedure: Transsphenoidal-adenectomy, Endoscopic pituitary surgery, Transcranial surgeries

Radiotherapy

External radiation is associated with significant side effects including hypopituitarism, optic nerve damage, neurological dysfunction, and increased risks of stroke and secondary brain tumours. Therefore, this option is reserved for:

- Patients not responding to DA therapy
- Patients not cured by surgery
- Malignant prolactinoma which are very rare

Hyperprolactinemia and pregnancy

- Serum PRL in pregnancy does not reliably reflect an increase in the size of prolactinomas.
- Microprolactinomas – Risk of clinically relevant tumour expansion is < 2% during pregnancy. Therefore, stop DA therapy as soon as pregnancy is confirmed. Advise patient to report for urgent assessment in the event of a severe headache or visual disturbance. Serial PRL monitoring is not necessary.
- Macroadenomas – Symptomatic tumour expansion occurs in 20–30% of women. Both options can be offered i.e. stopping the DA therapy when pregnancy is confirmed, with close surveillance; or continuing the DA in pregnancy.
- If visual field defects or progressive headaches develop, perform an MRI without gadolinium and restart a DA therapy if the tumour has grown significantly. Monitor visual fields every 2–3 months.
- If the enlarged tumour does not respond to DA therapy, alternatives options include trans-sphenoidal surgery if second trimester or defer surgery until delivery if third trimester.

Galactorrhoea without Hyperprolactinemia

Serum prolactin concentration is often normal in women who present with galactorrhea. Galactorrhea in the absence of hyperprolactinemia is not the result of any ongoing disease

Diagnosis - Ensure that the breast secretion is clear or milky. Next step is to measure the serum prolactin concentration. If the prolactin is elevated, the cause should be sought. If the prolactin is not elevated, there is no ongoing disease and no further tests are needed.

Treatment -

- Galactorrhea in the absence of hyperprolactinemia usually does not need to be treated, because it is not associated with ongoing disease and it is usually not bothersome.
- If the galactorrhea is bothersome, treat with a low dose of dopamine agonist, such as 0.25 mg of cabergoline twice a week.

Suggested Reading

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Journal Scan - I

Archana Minz[1], Juhi Bharti[2]
[1]Senior Resident, [2]Assistant Professor, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi

Journal of Gynecological Endocrinology 2019 Aug;35(8):695-700 Doi: 10.1080/09513590.2019.1576620

Comparison of the effect of two combinations of Myo-inositol and D-chiro-inositol in women with polycystic ovary syndrome undergoing ICSI: a randomized controlled trial

Nicolas Mendoza, Maria Paz Diaz-Ropero, Miguel Aragon, Vicente Maldonado, Placido Llaneza Juan Lorente, Raquel Mendoza-Tesarik, Jose Maldonado-Lobon, Monica Olivares and Juristo Fonolla

Study Objective : In infertile women with polycystic ovarian syndrome (PCOS) undergoing ovulation induction use of inositol in various forms or combinations or doses have improved reproductive outcomes during ICSI. Inositol has two major stereoisomers: **Myo-inositol (MYO)** and **D chiro-inositol (DCI).** Myo-inositol increases clinical pregnancy rate, improves metabolic profile and hyperandrogenism. However, Myo-inositol supplements alone are not sufficient to improve oocyte maturation, embryo quality and pregnancy rate. Nicolas et al evaluated the effect of two doses of DCI in combination with MYO in PCOS women undergoing ICSI.

Design : Nicolas Mendoza et al conducted this study at five sites in Spain from February 2016 to April 2017, the study was a double-blind, multicenter randomized clinical trial (RCT) which included women aged between 18 and 40 years with PCOS according to the Rotterdam criteria with a body mass index (BMI) <30 undergoing ICSI.

Measurements and Results : The investigators randomized 60 subjects, 30 each into study and control groups. The study group (SG) n=30 was administered oral soft gelatin capsules of 550 mg of MYO + 150 mg of DCI twice daily (3.6 :1) and the control group (CG) n=30 was administered 550 mg of MYO + 13.8 mg of DCI twice daily (40:1) over 12 weeks until the day of oocyte retrieval. There was no differences at baseline between the two groups regarding age, BMI, testosterone and HOMA –IR. Percentage of exclusions due to the risk of OHSS was lower in the study group (3.84% vs. 20.83%, p = .065). Duration of ovarian stimulation (SG = 10.48 ± 1.39 vs. CG =10.38 ± 0.86) and units of FSH used per cycle (SG = 1219.23 ± 102 vs. CG = 1137.5 ± 68) were comparable in both the groups. However, the pregnancy rate and live birth rates were significantly higher in the study group than in the control group (65.5% vs. 25.9% p = .003 and 55.2 % vs 14.8 % p=.002 respectively). There was significant difference in testosterone levels from the baseline to end of the study. However, the difference was similar in both the groups (Dif = 0.13; 95% (0.17, 0.08); p values < .001). Also, similar decrease in HOMA-IR was observed in both the groups (Dif = 0.70; 95%CI (1.23, 0.16); p = .011).

Conclusion : High doses of D chiro-inositol combined with Myo - inositol increases the percentage of pregnancy rates and reduces risk of OHSS in women with PCOS undergoing ICSI.

Comments : Inositol is a naturally occurring substance that increases pregnancy rate in women with PCOS by improving insulin sensitivity, increasing ovulation and reducing oxidative stress of follicular fluid. Combination of MYO:DCI at a ratio 40:1 showed better results than the administration of DCI or MYO alone. However,the ratio 40:1 though based on the physiological blood ratio of the two molecules in each tissue,was very low (13.8–27.6 mg/day) and insufficient to achieve adequate levels of DCI showing beneficial effect. Therefore, this study was performed comparing 40:1 ratio with other proposed MYO:DCI combinations containing higher dose of DCI and the results highlighted its importance in PCOS women undergoing ICSI. Further randomized studies are needed to justify better results with higher dose DCI.

Journal Scan - II

Rinchen Zangmo[1], Shainy[2]
[1]Assistant Professor, [2]Senior Resident, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi

Originally published 25 May 2019 https://doi.org/10.1161/JAHA.118.011501
Journal of the American Heart Association. 2019;8:e011501

Journal of the American Heart Association

Long Term Outcomes in Patients With Turner Syndrome: A 68 Year Follow Up

Margaret Fuchs, Christine Attenhofer Jost, Dusica Babovac-Vuksanovic, Heidi M. Connolly and Alexander Egbe

Background: Turner syndrome (TS) is the most common sex chromosome abnormality in women and is associated with increased morbidity and mortality. The authors describe long term outcomes in a large cohort of patients with TS.

Methods and Results: Fuchs et al performed a retrospective review of patients with TS followed at Mayo Clinic Rochester from 1950 to 2017. Clinical, imaging, surgical, and genetic data were analyzed. Survival analysis was performed with the Kaplan–Meier method using age and sex matched Olmsted County residents as the reference group. The study cohort comprised 317 patients with TS. Average age at diagnosis was 9 (range, 2–12) years, genetic testing was performed in 202 (64%), and pure monosomy X was present in 75 (37%). Congenital heart disease occurred in 131 (41%), with the most frequent lesions being bicuspid aortic valve (n=102, 32%) and coarctation of the aorta (n=43, 14%). Ascending aortic dilation was common, with mean aortic root size index 2 cm/m^2, and aortic dissection occurred in 6 (2%) patients. The average follow up was 11 (range, 2–26) years, yielding 3898 patient years, and during this period 46 (14%) patients died; mean age at the time of death was 53±17 years. The causes of death were cardiac (n=10, 22%), malignancy (n=5, 11%), gastrointestinal bleeding (n=4, 9%; ages 41, 47, 53, and 62 years), cirrhosis (n=2, 4%; ages 49 and 71 years), end stage renal failure (n=1, 2%; age 49 years), and unknown (n=24, 52%).

Patients with TS had reduced survival compared with the control group (82% versus 94% at 30 years; $P<0.001$), and the leading causes of death were cardiovascular disease, liver disease, and malignancy.

Conclusions: Patients with TS have multiorgan involvement resulting in multiple medical comorbidities. The overall survival is reduced in this population, and cardiovascular disease is the leading cause of mortality.

Comments: The current study by Fuchs et al provides important data on outcomes of Turner's syndrome. Although it is a retrospective study, it studied 317 patients over a period of 68 years. The data provided by the investigators is going to be very helpful to guide counseling of patients with TS. As majority of deaths according to this study is because of cardiovascular events, further studies are required to determine if targeted cardiovascular risk factor modification will result in improved survival in this population.

Forthcoming Events

- Next Monthly Clinical Meeting on 17th January, 2020 (4:00-5:00pm) at Dr Ram Manohar Lohia Hospital (RML).
- National FOGSI Conference -"Women's Reproductive & Sexual Health" on 29th February – 1st March, 2020 at the Lalit, New Delhi by Sir Ganga Ram Hospital under the aegis of FOGSI & AOGD.
- CME on "Endoscopy" on 15th February, 2020 & CME on "Infertility" on 16th February, 2020 organizing by MAMC under the aegis of AOGD & DGES.

Clinical Proceedings of AOGD Clinical Meeting held at Sir Ganga Ram Hospital, New Delhi on 27th December, 2019

Transverse Vaginal Septum: A Case Report

Punita Bhardwaj

Abstract

Transverse Vaginal septa are rare uterovaginal anomalies. It is an Autosomal recessive disorder which occurs due to the vertical fusion defect of the mullerian ducts. Classic Symptoms include Cyclic pelvic pain, Pain on defecation, Diarrhea and vomiting, Backache, Cryptomenorrhea, Irregular menses, Amenorrhea, Dysmenorrhea, Urinary retention, Haematuria, Dyspareunia, Infertility, on examination as routine, termination of pregnancy, pregnancy and labor. Diagnosis can be made by history, routine examination, ultrasound examination and MRI. This case report describes a case of a 10 yr old girl presented in outpatient with cyclical abdominal pain since 2 months with retention of urine. Local examination revealed a blind membrane and per rectal examination revealed a pelvic mass suggestive of imperforate transverse vaginal septum. On radiological examination showed transverse vaginal septum in upper one-third of vagina with less than 2 cm thickness. Surgical drainage of the old blood was done under laparoscopic guidance. Hysteroscopic release of uterine septum was done by a monopolar resectoscope. Post-operative dilatation of vagina was done to prevent restenosis. Laparoscopic guided abdominoperineal approach is better in such a case as treatment under vision can be carried out with minimal handling.

Case of Caesarean Scar Pregnancy-Misdiagnosed

Sharmistha Garg

Abstract

A 34 Yr old female PIL1 with previous LSCS came to OPD with complaint of continuous bleeding per vaginum since three months with history of suction and evacuation done twice in view of missed abortion in July 2018 and September 2019. Ultrasonography was done and was suggestive of *8X6 cm highly vascular mass adherent to anterior uterine wall? RPOC? A-V malformation*. MRI (pelvis) was done which also suggested same findings.

Patient was counselled regarding various modalities of treatment and as patient and her husband was very keen on uterus preservation plan and was made for uterine artery embolisation. Uterine Artery Embolisation was done on 21 October 2019 but patient started bleeding after that so patient was taken up for laparoscopic excision of anterior uterine wall with RPOC and repair o uterine defect on 23 October 2019. Histopathology reported *hyalinised chorionic villie suggestive of RPOC*.

Post-operative period was uneventful and after 4 weeks of follow-up patient is doing fine and her bleeding has stopped completely.

Postmenopausal choriocarcinoma: A rare case report

Indrani Ganguli, Mala Srivastava, Mamta Dagar, Tarun Kumar Das

Abstract

Choriocarcinoma is a highly malignant epithelial tumor originating from trophoblast. It primarily occurs during the fertile period. Postmenopausal uterine choriocarcinoma is very rare. We present a case of choriocarcinoma in a 52 year old postmenopausal lady developing 1 year after menopause. She presented with pain in lower abdomen. Frozen section reported poorly differentiated carcinoma of uterus. Bilateral pelvic and paraaortic lymphadenectomy with total omentectomy was done.

Histopathology revealed Choriocarcinoma. Serum beta-hCG was 510852 mIU/ml. She presented after 2 weeks with 3X3 cm soft mass at vault, bleed on touch. EMACO started. 5 cycles given. She has been continuing with treatment.

No obvious vault growth is seen which was evident easier.

Keywords: Uterine choriocarcinoma, postmenopausal bleeding, beta-hCG

Unique Complication of Pre-Eclampsia Syndrome: Intra-Cerebral Hemorrhage

Sakshi Nayar, Chandra Mansukhani, K Gujral

Cerebrovascular accidents are rare entity in pregnancy with hypertension, but causes high morbidity and mortality. Total incidence of cerebrovascular accidents in pregnancy is 10 to 34 per 100,000 deliveries. In Taiwan, a nationwide 13 years population based matched cohort study was done to identify the incidence of ICH in women with PIH. The incidence rate of ICH in patients with gestational hypertension as against their matched cohorts was 2.89 vs. 0.78 per 10,000 person-years, 3.72 fold higher. The incidence rate of ICH in pre-eclampsia was 6.61 vs. 0.80 per 10,000 person-years, 8.21 fold higher. Here we present two unusual cases of spontaneous intracerebral haemorrhage in pre-eclampsia which were managed conservatively. Case 1 Mrs. X, 28 year old, Primigravida flew alone from Mumbai at 26 weeks of gestation. Same night, she had diarrhoea and was found to be hypertensive at a near-by hospital. Admission was advised but was refused by the patient. When she did not wake up from her sleep, her attendants found her to be incoherent and brought her to Sir Gangaram Hospital. At the hospital, she was found to be agitated, incoherent and had a blood pressure of 170/118 mm Hg with urine albumin 3+. She was stabilized, relevant investigations sent, injectable anti-hypertensive and injection magnesium sulphate given and patient shifted to HDU. All initial investigations was suggestive of HELLP syndrome. After 6 hours, Inspite of normal blood pressure on anti-hypertensives, she was incoherent, hence, emergency NCCT head was done which revealed intracranial bleed in the genu of corpus callosum. Neurosurgery opinion was taken and she was started on conservative management. LSCS was done in view of maternal interest and patient improved on conservative management. Case 2 Mrs Y, 25 year old G2A1, referred as a case of 32 weeks with severe pre-eclampsia with fetal growth restriction with absent end diastolic flow in fetus. Patient was started on anti-hypertensive and dexamethasone cover was given. Patient underwent LSCS in view of poor biophysical score of 4/8 after dexamethasone cover in general anaesthesia due to failed spinal anaesthesia. Post operatively, patient was given injection magnesium sulphate till 24 hours of delivery. She had an uneventful recovery with foley's catheter out on day 2 and dressing done on day 3. Post operative day 4, patient complained of intractable headache for which MRI brain was done which revealed a 7x8cm hematoma in the right temporal and occipital lobe with a midline shift of 7mm. Neurosurgical opinion was taken and patient was managed conservatively with NCCT head done every alternate day till hematoma resolved.

ICH in pregnancy with hypertension is a therapeutic emergency. Rapid treatment helps reducing neurological morbidity and complete recovery. Obstetricians should be very cautious in the cases of PIH, as high blood pressure with persistent headache can be ICH; which requires additional prompt brain imaging and neurosurgical evaluation.

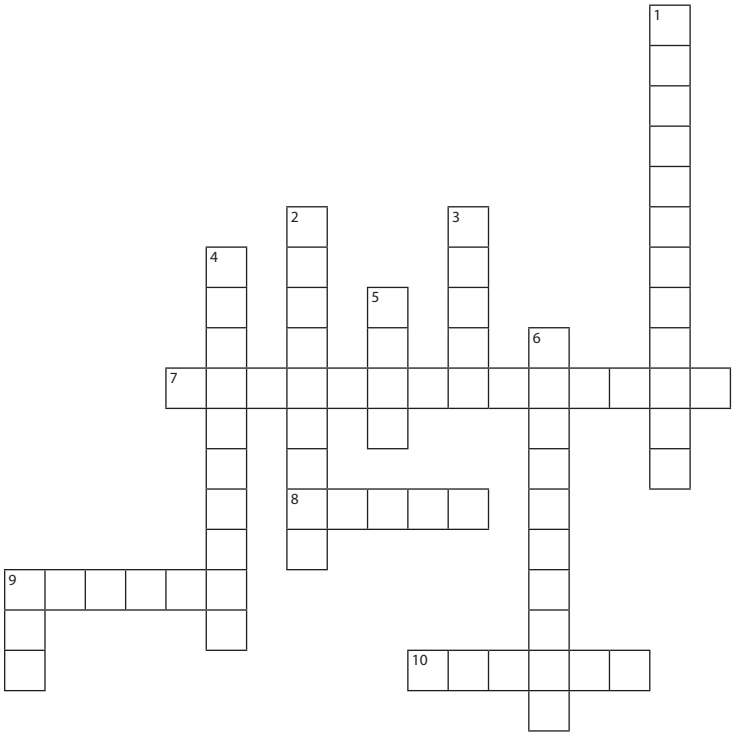
Answer: December Issue

1. c.	6. d.	11. a.	16. b.
2. a.	7. d.	12. c.	17. a.
3. b.	8. a.	13. a.	18. a.
4. b.	9. a.	14. d.	19. a.
5. b.	10. a	15. c.	20. d.

The Maze of Knowledge

Anju Singh
Assistant Professor, Department of Obstetrics & Gynaecology and Urogynaecology, All India Institute of Medical Sciences, New Delhi

CROSSWORD



Down:

1. _____ contributes to increased cardiovascular risk in PCOS patients.
2. _____ enzyme is involved in conversion of testosterone to estrogen.
3. Free Androgen index uses values of _____ testosterone and SHBG.
4. Which SSRI is FDA approved for treatment of menopausal symptoms.
5. _____ is the most common cause of androgen excess in women.
6. _____ agent is for treatment of moderate to severe dyspareunia caused by vulvovaginal atrophy in postmenopausal women.

Across:

7. Y chromosome material increases the risk of _____ in dysgenetic gonads.
8. _____ tool used for screening of eating habits
9. _____'s questionnaire is used for screeing of obstructive sleep apnea.
10. On TVS (Frequency Bandwidth 8 MHz), how many follicles should be seen for diagnosis of PCOS.

PICTORIAL QUIZ

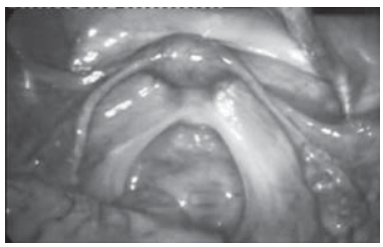
Q2. Following is the laparoscopic finding of the patient who presents to OPD with primary amenorrhea with no secondary sexual characteristics.

1. Identify the condition.

   _____

2. What will be the karyotype of the patient and gene involved?

   _____



Watsapp your answers to **9211656757.**
Names of first three correct entries will be mentioned in the next issue

Refer page 48 for previous answer key.

Royal College of Obstetricians & Gynaecologists

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- MRCOG part 2 Revision Course bi-annually
- MRCOG Part 3 Practical Course Franchised bi-annually
- MRCOG part 3 Practical Course Non- Franchised bi-annually

MRCOG EXAMINATION

- MRCOG Part 1 & 2 Conducted Annually
- MRCOG Part 3 examination conducted bi-annually

WORKSHOPS

- ISCCP Colposcopy and Leep Workshop bi-annually

SIMMS BLACK TRAVELLING FELLOWSHIP UK

- Conducted Annually at Delhi and other regions of North Zone

CONFERENCES

- Multidisciplinary, Evidence - Based National Conference Annually

PHILANTHROPIC ACTIVITY

- Breast and Cervical Cancer Screening Awareness Camp Annually
- Cervical Cancers Vaccination Camp bi-annually
  (More Than 1000 Girls and Women Vaccinated Free Of Cost)

RCOG WORLD CONGRESS

- Annual representation by AICC RCOG North Zone Fellows & Members

FORTHCOMING ACTIVITIES

- Early Pregnancy Scan Workshop

Mailing Address:

RCOG North Zone Secretariat

OT Complex 3rd Floor, Sant Parmanand Hospital, 18 Shamnath Marg, Civil Lines, Delhi 110054

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