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AOGD BULLETIN

AOGD Theme 2017-18

'Optimizing Women's Health Through Enhanced Skills and Best Practices'

Issue:

Hormones in Gynecology

AOGD SECRETARIAT

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President's Message

Dear Friends

At the outset I must thank you all for the heady success of the **'39th Annual Conference of AOGD**' held recently at India Habitat Centre. Congratulatory messages kept pouring in for several days after the conference and we are still in a state of euphoria. We are humbled by the heartfelt appreciation and encouragement that we received from well-wishers and thank you once again for partaking enthusiastically in AOGD's most awaited annual event. The attendance was outstanding (literally & figuratively), academics superlative, weather unbeatable and food heavenly – what else can one ask for! There were good interactions and discussions in almost all sessions and the newly introduced 'Best of 2017' format was informative and refreshing. Orations, panel discussions, key note addresses, symposia, video sessions, debates and controversies served to update members on a variety of contemporary issues. International, National and Delhi faculty need special applause for their time and effort spent on making the sessions valuable.

AOGD 2017-18 prides itself in conferring **'Lifetime Achievement Awards'** for the first time in the history of AOGD to the two doyens of AOGD, Dr. SN Mukherjee and Dr. Urmil Sharma. Both are pillars of this organisation having supported and nurtured it to its present status. We also felicitated our patrons Prof. Kamal Buckshee and Prof Neera Agarwal for their unfailing patronage at all times. The efforts of AOGD committee chairpersons did not go unrecognised and all 13 Chairpersons were felicitated at the Inauguration. The untiring energy of the committees and their members made possible the release of the much awaited **'AOGD Good Practice Guidelines'** book. The unique role play on ***'Violence Against Doctors'*** received a standing ovation and we have requests to put it up on YouTube which may be eye-opening in the aftermath of the recent twin controversy. Doctors have become scapegoats and easy targets for slaughter and as an association we must stand-up against this. Readers can send in their suggestions and AOGD can serve a response to the press and government.

This issue on '**Hormones in Gynecology'** guides you through various clinical situations and their hormonal management; puberty disorders, AUB, menopause and hyperprolactinemia (where there's always a dilemma on how long to continue dopamine agonists). An update on SPRMs, SERMs, Dienogest and an insight into the mysteries of the Pineal gland makes for interesting reading. Also relive the Conference, Precongress works, October and November events through colourful photographs and captions!

Cheers and Wishing you all a Happy, Peaceful & Healthy 2018!

Shalini Rajaram
President, AOGD (2017-18)

Vice President's Message

Dear Friends

After the successful completion of the annual AOGD conference mega event, it's still not the time to "hang our boots & relax". Other AOGD activities are round the corner and so is the next issue of our bulletin.

Hormones play a key role in maintaining the internal milieu of female and in all stages of development and function of female system. GnRH, FSH & LH from brain and estrogen & progesterone from ovaries & corpus luteum control the female reproductive system. They are the essence of female body and brain from puberty to menopause. Whereas their bizarre production can play havoc with female system; the natural & synthetic medicated forms can be savior for pregnancy disorders, AUB & post menopausal problems. The current issue deals with some of these problems.

So enjoy ready this issue basking in winter sun…

Cheers!

Kiran Guleria
Vice President AOGD (2017-18)

From the Secretary's Desk.....

Dear AOGDians

Hello!

Thank you for joining in large numbers & making the Annual Conference a grand success. I sincerely hope that you enjoyed yourself in acquiring knowledge.

The photographs & videos of conference are available on net; please go through our website www.aogd.org, click on the link to conference photos and videos and browse. This is also an opportunity for members who were not able to attend the conference; you can watch all the lectures and panels online through this link.

All the AOGD sub-committees contributed to make a handbook of **"AOGD Good Clinical Practice Guidelines"** which was distributed during conference. It will also be available shortly on our website. I am sure it will be very helpful in your day to day practice. I will try to get it printed and posted to all members.

So here we are with a new issue of bulletin concentrating on **"Hormones in gynecology"**. This is a tricky area for general gynecologist. We hope this will enable you to better understand hormone use in gynaecology.

This the season of peanuts, gur & basking in sun…Enjoy….

Thanks & Regards

Abha Sharma
Secretary AOGD (2017-18)

Monthly Clinical Meet

Monthly Clinical Meet will be held at Sir Ganga Ram Hospital, New Delhi on **Thursday, 29th December, 2017** from 4:00-5:00pm.

From the Editorial Board

Respected Seniors and dear friends,

Greeting from all of us at editorial board as we bring out the AOGD bulletin for December 2017. Hope you all enjoyed reading the ***Conference Proceedings*** and ***AOGD Good Clinical Practice Guidelines*** books as much as you enjoyed attending the 39th annual conference of AOGD last month. For those who couldn't attend the conference, the same have been posted on the AOGD website.

The present issue is on Hormones in Gynecology. As rightly said by someone

"If you control hormones you can control life"

A woman's life journey is basically all about the hormones. Issues start from the puberty where delicate balance between hypothalamus, pituitary ovarian axis has to be established and continue throughout the reproductive life and even beyond that. Every monthly menstrual cycle involves so much co- ordination between all these organs with resultant effects of hormonal on endometrium and other body organs including mood changes too. Every woman has to deal with these monthly changes. When something goes wrong issues of infertility, menstrual problems (AUB) arise. And once the menstruation stops, one has to battle the long postmenopausal journey of estrogen deficiency.

So the truth is ***"A Woman's life is not easy".*** And we have to have a good understanding of these important hormones to help our patients. Considering this we decided to bring out this issue with clinically relevant topics like puberty management, AUB, ovulation induction and Menopausal Hormonal Therapy. Newer evolving therapies like SERMs & SPRMs and Dienogest have also been discussed. Hope you all will enjoy reading through these topics and will find them useful in clinical practice.

Do attempt quiz in the end. All feedbacks are most welcome.

The Editorial Team
AOGD (2017-18)

Menopausal Hormone Therapy

Neerja Goel
Professor and Unit Head, SMS&R, Sharda University, Greater Noida

Menopause is defined as the time when ovaries cease functioning and menstrual periods stop, marking the end of reproductive years. Diagnosis of menopause is retrospective when a woman stops monthly period for 12 consecutive cycles. The average age of menopause in India is 48.5 ± 2 years. It may be spontaneous or induced through a surgery, chemotherapy or radiation. The total number of menopausal women in India is approximately 70-80 million. This number indicates the necessity of implementing menopause education. The average life of an Indian woman is 68-70 years, that means she spends nearly 20-30 years in postmenopausal period.

STRAW 2011 has divided entire life of a woman into three phases; reproductive (-5 to -3) perimenopuse (-2 to -1) and postmenopause (+1to +2). Final menstrual period is described as FMP or 0 stage. This 2011 ***STRAW (Stages of Reproductive Aging Workshop)*** is depicted in table 1[1]. Menopause earlier than 49 years occurs in women who are vegetarian, malnourished, African, hysterectomized, ligated, smokers and are living at high altitudes. Urban obese women with higher socioeconomic status with increased BMI, alcohol and non-vegetarian consumption have delayed menopause. Hence this group suffers from less postmenopausal symptoms.

Menopausal Health Issues

Menopause is a natural phenomenon but it is not normal. It is an estrogen deficient endocrinopathy which results in early, late and very late symptoms (table 2). The psycho-physiological symptoms such as hot flashes, mood changes, sleep disturbances and irritability are assessed by Kuppermann score[2] (table 3). Late physical changes e.g. sexual dysfunction, atrophic vaginitis are assessed by vaginal health index (table-4).[3] Later diseases like osteoporosis, CVD & Alzheimer's disease occur after 60 to 70 years.

Table 2: Symptoms of menopause.

Impact of estrogen deficient endocrinopathy		
Early Symptoms	Late Physical Changes	Later Diseases
Hot Flushes Insomia Irritability Mood disturbances	Sexual Dysfunction Stress Urinary Incontinence Connective Tissue Changes	Osteoporosis CVD Dementia (AD) Cancer

Postmenopausal stage of woman is also marked as start of many multisystem disorders and various cancers e.g. breast cancers and genital cancers. So the woman needs careful assessment by a specialist or a group of specialists e.g. physician, ophthalmologist, oncologist & endocrinologist along with a trained gynecologist.

Table 1: Stages of Reproductive Aging Workshop STRAW 2011.

Stage	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1C	+2
Terminology	REPRODUCTIVE				MENSTRUAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Pate		Early	Late	Early			Late
					Perimenopause					
Duration	Variable				Variable	1-3 years	2 years (1+1)	3-6 years	Remaining lifespan	
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow length	Variable length Persistent[3]7- day difference in length of consecutive cycles	Interval of amenorrhea of[3]60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable Low Low	Variable Low Low	>25 IU/L Low Low	Variable Low Low	Stabilizes Very low Very low		
Antral follicle count			Low	Low	Low	Low	Very low	Very low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms likely	Vasomotor symptoms most likely			Increasing symptoms of urogenital atrophy

Table 3: Modified Kuppermann Index.

Symptoms	Weighting factor	Severity scale 0	Severity scale 1	Severity scale 2	Severity scale 3
Sweating Hot flashes	x4	None	<3 times/day	<3 times/day	≥ 10 times/day
Paresthesia	x2	None	Relationship with climate	Frequent tingling, burning, pricking or numbness	Loss of sense of warm and pain
Insomnia	x2	None	Once in a while	Frequent need sleeping pill	Affects life and work
Nervousness	x2	None	Once in a while	Frequent	Frequent cannot control
Melancholia	x1	None	Once in a while	Frequent, can seif control	Losing faith in life
Vertigo	x1	None	Once in a while	Frequent	Affects daily life
Fatigue	x1	None	Once in a while	Feel difficult when climbing the 4th floor	Affects daily life
Arthralgia Myalgia	x1	None	Once in a while	Frequent, not affecting function	Affects function
Headache	x1	None	Once in a while	Frequent	Requires treatment
Heart palpitation	x1	None	Once in a while	Frequent, not affecting daily life	Requires treatment
Formication	x1		Once in a while	Frequent	Requires treatment
Sexual complaints	x2	Normal	Reduced libido	Sexual problems	Loss of libido
Urinary tract infection	x2	None	Once in a while	More than 3 times per year, not requiring medication	More than 3 times per year, requiring medication

Table 4: Modified Vaginal Health Index.

Parameters	1	2	3
• pH	> 6.5	5 - 6.5	< 5
• Moisture/ Consistency of fluid	No	Minimal	Normal
• Rugosity	None	Minimal	Good
• Elasticity	Poor	Fair	Excellent
• Length of vagina	< 4	4-6	> 6
• Thickness of vagina	Papery thin	Thin	Normal
• Epithelial Integrity	Petechiae	Petechiae after scraping	Normal
• Vascularity	Minimal	Fair	Good

Hormonal Changes

There is reversal of hormonal milieu after menopause. Out of three estrogens; estradiol (E2) is 80 times more portent than estriol (E3). Estrone (E1) is the least potent. There is reversal of estradiol (E2) estrone (E1) ratio. Estrone is the predominant hormone during menopause due to peripheral conversion from androstenedione. Other hormones which increase include FSH, LH and testosterone. There is decrease in estradiol and inhibin B. FSH rise is more than LH as the half life of FSH is longer with delayed clearing.

Menopausal Hormonal Therapy

When to Give?

According to Indian menopause society every post menopausal woman is a potential candidate for ***menopausal hormonal therapy (MHT) till the age of 60 years***. This life span from menopause to 60 years is named as ***'window of opportunity'***. The definite indications of MHT include peri and post menopausal hot flashes, urogenital symptoms, surgical menopause, osteoporosis and diminished quality of life. However, the contraindications such as liver diseases thromboembolism, breast cancer, endometrial cancer and unexplained vaginal bleeding should be ruled out.

What to Give?

Menopausal hormonal therapy consists of estrogens, progestogens and androgens. Natural estrogen e.g. conjugated equine estrogen, 17 –β estradiol and estradiol valerate are preferred. Progestogens which are metabolically friendly e.g. dydrogesterone, medroxyprogesterone acetate and micronized progesterone are to be used with estrogens. Androgens are reserved for increasing libido and sexual desire. Testosterone sachet and transdermal patches are used.[4] The regime of estrogens and progestogens are depicted in Table 5.

Table 5: Regimens of Estrogen, Progestogens Therapy

Regimens	Estrogen	Progestogen	Bleeding patterns
Estrogen only therapy	Daily	Not given	Nil
Cyclic sequential	1-25	16-25	Withdrawal
Cyclic combined	1-25	1-25	Breakthrough
Continuous sequential	1-30	1-12	Breakthrogh
Continuous combined	1-30	1-30	Nil
Long cycle hormone therapy	1-70	71-84	4/Year

Role of estrogen is mainly to allay menopausal symptoms. Lowest effective dose is started i.e. ***.375 mg to .625 mg of conjugated equine estrogen***. Progestogens are given in women with intact uterus to oppose the effect of estrogen on endometrium for prevention of endometrial

hyperplasia. Usually ***10mg of Dydogestorne for 10 days*** in sequential course and 5mg daily in continuous combined course is given.

Screening & Follow Up

Before starting MHT there are certain pretreatment investigations which need to be carried out. These include complete blood count, urine culture, blood sugar, lipid profile, pap smear, transvaginal sonography mammography and DEXA scan. Regular follow up is required in women on MHT. First follow up is done at 3 months to confirm the compliance and to monitor the side effects. Subsequent follow ups are done at 6 months and then yearly intervals where patient is asked for symptom relief. Repeat biochemical test are done yearly. Two yearly mammography and transvaginal sonography is carried out. These investigations are also carried out as a base line work up after the age of 50 years whether she is receiving MHT or not.

Regarding the duration of MHT it has been advised to give estrogen only therapy upto 7-10 years in hysterectomized women and estrogen progestin therapy should not exceed more than 5 years. It is the progestin component which increases the risk of breast cancer.

Evaluation of endometrium is more intense in presence of irregular bleeding and bleeding after six months of amenorrhea and bleeding which does not respond to hormonal manipulation. In such cases transvaginal sonography and saline infusion sonography is done. If it is more than 8mm, sampling is advocated. MHT is discontinued in a gradual manner over a period of a month.

Newer Options for HRT

Newer drugs have been added to MHT schedule. A combination of 17-β estrodiol (1 or 2 mg) with dydrogestrone 5 or 10 mg ***as Femoston Plain & Femoston Conti*** is available. This molecule has advantage of being more metabolically friendly. Femoston Conti is given daily where as Femoston Plain is given as a continuous sequential manner.

Amongst the other new entries fourth generations SERMs bazedoxifene with low dose conjugated equine estrogen (***APRELA***) has been added for women beyond 60 years. The dose of single tablet is once a day for 2 to 3 years. It does not cause hot flashes and vaginal atrophy contrary to 3rd generation SERM like raloxifene. ***Tibolone*** is another synthetic steroid having 2 estrogenic and 1 progestogenic and 1 androgenic metabolite. It has an additional advantage of allaying decreased libido and sexual desire. The dose is 2.5 mg daily. Tibolone has controversial effect on breast cancer so it should not be given for longer period.[5]

Phytoestrogens e.g. isoflavones, lignans, coumestens have protective effect on osteoporosis and hot flashes. Although the potency of isoflavones as compared to estrogens is far less, they are indicated whenever estrogen is contraindicated. The natural sources are soy products, red clover and beans.

Another drug which is adjunct to MHT is **Sulbutiamine**. This is a thiamine derivative having an antiasthenic property. It cures mental, physical, emotional and sexual asthenia. The dose is 100-200mg per day and it can be given continuously.

MHT & Weight Gain Concerns

There is no weight gain with menopausal hormonal therapy rather the weight is redistributed and muscle mass is increased as estrogen is anabolic in nature. The sarcopenic obesity of menopausal lady is cured to some extent by taking selective protein rich diet in ornithine leucine, isoleucine and low calorie diet with weight bearing exercises.[6]

Menopause is no longer considered an empty nest syndrome. It is the age when woman is free from small children's worry, their education, carrier and job problems. She herself is a capable woman. She should cultivate new hobbies and reignite old passions. This could be the time for self discovery, creativity and wisdom. Self reflection and redefinition is what is required.

Case scenarios

1. Forty two year old early perimenopausal lady, nonsmoker, nonhypertensive not ligated complaints of 7-8 hot flashes per day. Her routine work is disturbed. What is the best treatment?

   Ans: Low dose oral contraceptive pill till the age of 45 years.

2. A 48 years old late perimenopausal woman complaints of 8-9 hot flashes per day with incapacitation of work. No family history of cancer or medical disease. What is the best treatment for her?

   Ans: Cyclic sequential regime with counseling that she will have withdrawal bleeding along with general guidelines.

3. A 52-year lady comes with history of hot flashes for 1 year. She had breast cancer and TAH+BSO 1year back for tamoxifen induced endometrial hyperplasia. What is the best option?

   Ans: MHT can not be given to such patients. The best choice is Gabapentin in the doses of 300-1200 mgs. In small, node negative, unilateral lesions estrogen therapy can be given for a short while after 1 year.

4. A 52-year-old postmenopausal lady comes with bleeding on MHT. She was taking continuous combined regime. What is the advice?

   Ans: It is a break through bleeding. Transvaginal sonograghy is advised and if the ET is> 8mm endometrial sampling is advised. If normal, switch over to cyclic sequential regime.

5. 55 years old lady complaints of wrist fracture. On DEXA scan she has severe osteoporosis. She also has lordosis and loss of height. What is the treatment?

   Ans: Diet, Calcium, Vitamin D, Idrofos 150 mg per month with weight bearing exercises are advised.

MHT can also be given in continuous combined regime for 3-5 years.

6. An 80-year-old lady comes with osteoporosis with history of knee replacement. She is walking with walker. She also has memory loss also. What is the recommended treatment?

   Ans: Raloxifene, a third generation SERM in the dose of 60 mg per day is the drug of choice. Mental exercises with micronutrients are to be advised.

7. 58 years' lady complaints of wrinkling of hands and face and widening of partition of hair line. She has facial hair growth also. She wants to know the treatment.

   Ans: Plenty of water intake, avoidance of sun and blowers, facial massage, spa, hair massage, anti androgens, selenium anti oxidants, minoxidil and hair transplant.

8. 62-year-old female complaints of vaginal dryness, itching, loss of libido and sexual dysfunction. What is the best treatment?

   Ans: Evalon vaginal cream, 0.5 mg HS x 6 weeks, Tibolone 2.5 mg OD, testosterone transdermal patch OD.

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Day of the Month:

World AIDS Day (1st December)

World AIDS Day takes place on the 1st December each year. It's an opportunity for people worldwide to unite in the fight against HIV, to show support for people living with HIV, and to commemorate those who have died from an AIDS-related illness. Founded in 1988, World AIDS Day was the first ever global health day. World AIDS Day is one of the eight official **global public health** campaigns marked by the **World Health Organization** (WHO) and is observed by all UN member states

Globally, there are an estimated 36.7 million people who have the virus. Despite the virus only being identified in 1984, more than 35 million people have died of HIV or AIDS, making it one of the most destructive pandemics in history. Thanks to recent improved access to **antiretroviral treatment** in many regions of the world, the death rate from AIDS epidemic has decreased since its peak in 2005. There are laws to protect people living with HIV and we understand so much more about the condition. Despite this, people do not know the facts about how to protect themselves and others, and stigma and discrimination remain a reality for many people living with the condition. World AIDS Day is important because it reminds the public and government that HIV has not gone away – there is still a vital need to raise money, increase awareness, fight prejudice and improve education. World AIDS Day is an opportunity to show solidarity with the millions of people living with HIV worldwide. Most people do this by wearing an HIV awareness red ribbon on the day.

In 2016, a collection of HIV and AIDS related **NGOs** started a campaign to rename World AIDS Day to World HIV Day. They claim the change will put the emphasis on social justice issues, and the advancement of treatments. In US, **White House** began marking World AIDS Day with the iconic display of a 28 foot (8.5 m) AIDS Ribbon on the building›s North Portico in 2007. On November 30, 2017, President **Donald Trump** proclaimed *World AIDS Day* for December 1.

All the World AIDS Day campaigns focus on a specific theme. Each year's theme is chosen by the Global Steering Committee of the World AIDS Campaign (WAC).

World AIDS Day Themes

2017	My Health, My Right
2016	Hands up for HIVprevention
2015	On the fast track to end AIDS
2014	Close the gap
2013	Zero Discrimination
2012	Together we will end AIDS
2011	Getting to Zero
2010	Universal Access and Human Rights

LET'S END IT: End isolation, End stigma, End HIV transmission

Disorders of Pubertal Development

Abha Sharma
Specialist, Deptt of Obst & Gynaecology, GTB Hospital, Delhi

Puberty is an evolving sequence of maturational steps in a well defined pattern lasting over a period of 4.5 years on an average (Range 1-5 yrs). The cardinal events of puberty with their order of emergence are-

- Growth Spurt-Starts around 8 years with peak velocity around one year before menarche
- Thelarche- Breast growth, starts around 8-9 years
- Pubarche-Growth of pubic and axillary hair, starts around 8-9 years
- Menarche-Onset of menses. Occurs on an average of 2.6 years after onset of pubarche and thelarche

The average age of puberty and menarche is declining world wide and in India has been reported to be from 12.4 years to 13.7 years

Disorders of Pubertal Development can be precocious puberty or Delayed Puberty.

Precocious puberty

In premature growth and puberty, spontaneous onset of puberty occurs more than two standard deviations earlier than normal mean age of onset. Taking 10 years as the average age of onset, precocious puberty is defined as secondary sexual development before the age of 8 years. Puberty begins with activation of the hypothalamic-pituitary-gonadal system.

The diagnostic evaluation necessarily involves the differentiation of pathological disorders from the normal variants of early puberty. The age of 6-8 years falls in grey zone and requires judicious use of investigations to diagnose normal variations.

Pathological conditions in which puberty occurs early are divided into gonadotropin-dependent disorders (**true precocious puberty**) and gonadotropin-independent disorders (**precocious pseudopuberty**). A further possibility to be considered is isolated premature appearance of pubic hair or breast development (**Incomplete precocious puberty**)

***Evaluation*:** Thorough **history** including sequence of development of secondary sex characters, whether isolated, Family history of onset of puberty, any h/o head trauma, headache, seizures, abdominal pain etc

Examination- Height, weight, skin examination for café au lait spots, Tanner staging for breast and pubic hair, fundus and visual field examination

A simple plan for evaluation of a case presenting with premature development of secondary sex characters is given in Figure 1

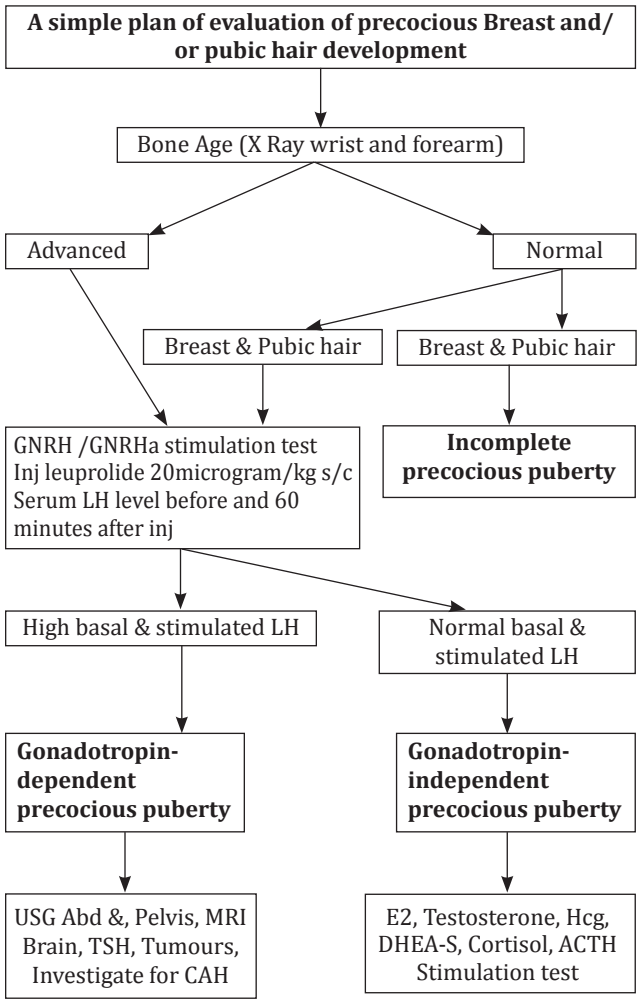

Figure 1: A simple plan of evaluation of precocious Breast and/or pubic hair development

Gonadotropin-Dependent Precocious Puberty (True Precocious Puberty)

Gonadotropin-dependent precocious puberty is initiated by premature activation of the hypothalamic-pituitary-gonadal axis. Sequence of pubertal development remains normal i.e breast development precedes vaginal bleeding.

- The cause of precocious puberty remains unidentified in up to 90 % of girls (**Idiopathic**).
- **Organic lesions** in the hypothalamic and pituitary area like hamartoma, glioma, astrocytoma, germinoma

and autonomous pituitary gonadotropin-secretory tumour

- It can also occur in children with internal hydrocephalus or other lesions of the central nervous system, such as an earlier episode of **meningitis or traumatic brain injury** or prior radiotherapy to the head.
- **Primary severe hypothyroidism** and exposure to high circulating androgen or estrogen as may occur with Congenital Adrenal Hyperplasia (**CAH), virilising tumours** and **McCune Albright syndrome** may also present with precocious puberty.

In true precocious puberty, treatment is indicated because of the major psychosocial stress on the affected child resulting from the very early appearance of signs of puberty, the frequent (and generally wrong) assumption by others that the child possesses a correspondingly early mental and emotional "maturity," and the risk of reduced adult height due to disproportional acceleration of skeletal age.

Treatment

The treatment involves administration of **GnRH analogs** that suppress the effects of the elevated gonadotropins LH and FSH through down-regulation of the pituitary GnRH receptors. Physical examinations during treatment reveal the slowing or cessation or sometimes even a return of the prepubertal stage; on biochemical testing, the gonadotropins LH and FSH as well as the sex steroids estrogen or testosterone are detectable only in very low concentrations, or not at all. In doubtful cases, a GnRH test can be performed during the trough just before the next scheduled GnRH injection, in order to determine whether the gonadotropins have been adequately suppressed. If basal and/or stimulated LH and FSH are measured in higher concentrations, then GnRH analogs should be given at a higher dose or at shorter intervals.

- Leuprolide 3.75 – 7.5 mg monthly or 11.25 mg 3 monthly
- Triptorelin 3.0-3.75 mg monthly or 11.25 mg 3 monthly

The pubertal stage, height, and skeletal age of the patient should be monitored over the course of treatment. The treatment of true precocious puberty should be terminated when it is time for normal puberty to begin, and when it can be expected that the patient will attain an optimal adult height

Gonadotropin-Independent Precocious Puberty (Precocious Pseudopuberty)

Precocious pseudopuberty arises, by definition, before and independently of the maturation of the hypothalamic-pituitary-gonadal axis. It can result from excess sex steroid secretion from the gonads, adrenals or from exposure to exogenous estrogens. Sequence of pubertal development may be abnormal i.e vaginal bleeding may precede breast development.

- Autonomous **functional ovarian cysts** are the most common cause and present with transient breast development or vaginal bleeding. These can be self-limited in most and require no treatment.
- **Ovarian tumours** like granulosa cell tumors,Leydig cell tumors and gonadoblastoma are rare causes
- It can also be due to external factors, such as the therapeutic or accidental ingestion of estrogens or androgens, or a large number of environmental pollutants.
- Adrenal pathology such as androgen secreting tumors or **Congenital Adrenal Hyperplasia**
- **McCune Albright Syndrome** is a rare genetic disorder presenting with characteristic precocious puberty, café au lait skin spots and fibrous dysplasia of bone

Treatment

Treatment is aimed at the underlying pathology. Functional cysts if persist can be removed laparoscopically. Other tumours of ovary and adrenals can be treated surgically. Congenital adrenal hyperplasia requires treatment with glucocorticoids and those with McCune Albright Syndrome need drugs that inhibit steroidogenesis. **These patients should be referred to endocrinologist.**

Incomplete Precocious Puberty

Incomplete Precocious Puberty includes premature pubarche or thelarche i.e isolated breast or pubic hair development and is usually a variant of normal puberty. They still merit close follow up as up to 20 % girls later develop gonadotropin dependent precocious puberty.

Premature pubarche may be a feature of CAH which needs to be ruled out if bone age is advanced. Most children only need counselling , reassurance and follow up.

Delayed Puberty

When growth and puberty are constitutionally delayed, puberty spontaneously begins at a time that is more than two standard deviations later than the mean time of breast development in girls effectively 12 years.

Causes:

- **Constitutional delay** (10%)– Family history of delayed puberty, Excessive exercising
- **Hypergonadotropic Hypogonadism** (43%)- Gonadal Dysgenesis eg Turner syndrome, radiation or chemotherapy
- **Hypogonadotropic Hypogonadism** (21%)-

Hyperprolactenemia: pituitary adenomas, Hypothyroidism, Anorexia, Chronic illness like inflammatory bowel disease or liver diseases

- **Eugonadism** (26%): These present with absence of menarche rather than with delayed puberty . Causes are Mullerian anomalies and Androgen Insensitivity Syndrome. When in doubt an ultrasound of pelvis will confirm the diagnosis.

Evaluation: Simple plan of management for delayed puberty is given in figure-2

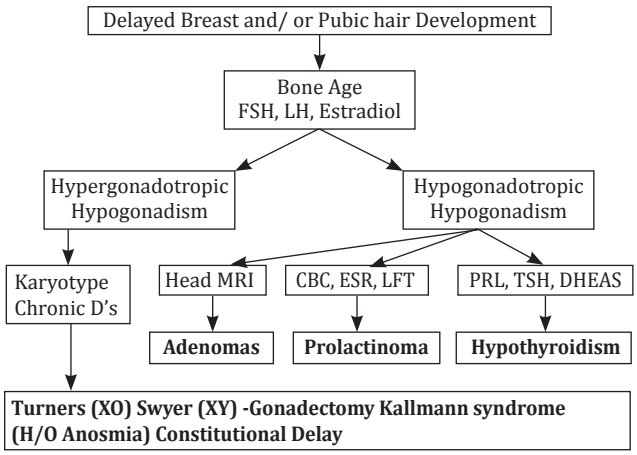

Figure-2: Evaluation for Delayed Puberty

Treatment

Recognition of physiological delay requires only reassurance and follow up. Correction of the specific cause is first priority.

The goals of short term sex hormone therapy are to foster age appropriate secondary sexual development and to induce a growth spurt and increase bone density without causing premature epiphyseal closure. Bone age should be monitored six monthly.

Treatment is started with micronized estradiol alone oral (.25-.5 mg) or transdermal patch. Continue for 6 to 12 months till substantial breast growth has occurred or patient starts getting period, then progesterone is added. This may need to be continued long term in patients of isolated GnRH Deficiency or gonadal dysgenesis.

Conclusion

The diagnosis of abnormal puberty requires thorough knowledge of normal pubertal development and of the variations of normal puberty as well as its pathology. A detailed history is the first step in the diagnostic evaluation of a normal variant or an abnormal puberty. Further evaluation includes laboratory testing (estradiol, testosterone, and the results of a GnRH test, among others) and imaging studies (x-ray of the left hand and wrist, ultrasonography of the gonads, magnetic resonance imaging). Treatment is directed at both the acute and the long-term consequences of precocious, markedly delayed, or absent pubertal development.

Disorders of pubertal development should be recognized early, correctly diagnosed by a pediatric endocrinologist, and appropriately treated

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Calendar of Monthly Clinical Meetings 2017-2018

Months	Name of the Institute
29th December 2017	Sir Ganga Ram Hospital
19th January 2018	Dr RML Hospital
23rd February 2018	Lady Hardinge Medical College
23rd March 2018	UCMS & GTB Hospital
27th April 2018	Apollo Hospital, Sarita Vihar

SOP: Hyperprolactinemia

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- Nonpuerperal hyperprolactinemia is caused by lactotroph adenomas (prolactinomas), which account for approximately 40% of all pituitary tumors.
- Hyperprolactinemia may also develop due to pharmacological or pathological interruption of hypothalamic-pituitary dopaminergic pathways and is sometimes idiopathic.
- It is seen in 10-25% of women with secondary amenorrhea, 30% women with galactorrhea and 75% with amenorrhea and galactorrhea.

Causes of Hyperprolactinemia

Physiological
Pregnancy
Puerperium
Neonatal period
Stress
Sexual Intercourse
Exercise
Chest wall
Breast stimulation
Inadequate sleep

Drug Induced
Anesthetics
Anticonvulsant
Antidepressants
Antihistamines (H2)
Antihypertensives
Cholinergic agonist
Drug-induced hypersecretion
Catecholamine depletor
Dopamine receptor blockers
Dopamine synthesis inhibitor
Estrogens: oral contraceptives; oral contraceptive withdrawal
Neuroleptics/antipsychotics
Neuropeptides
Opiates and opiate antagonists

Pathological
Pituitary: Prolactinomas
"Empty sella" syndrome
Acromegaly
Hypothalamus: Non functioning pituitary adenomas
Meningiomas
Craniopharyngiomas
Sellar or parasellar masses
Dysgerminomas
Neurogenic: Chest wall lesions
Spinal cord lesions
Inflammatory/ Granulomatous: Histiocytosis
Sarcoidosis
Chronic renal or hepatic failure
Primary hypothyroidism
PCOS
Miscellaneous: Paraneoplastic
Ectopic sources of prolactin secretion
Idiopathic

Diagnosis of Hyperprolactinemia

- A single measurement of serum prolactin above the upper limit of normal confirms the diagnosis as long as the serum sample was obtained without excessive venipuncture stress.
- When in doubt, sampling can be repeated on a different day at 15 to 20-min intervals to account for possible prolactin pulsatility
- **Prolactin Levels are assay specific, (Normal <25 ng/mL for most laboratories)**

Macro Prolactin –Serum PrL elevation secondary to reduced clearance of this complex of PRL, IgG causes pseudohyperprolactinemia

MacroPRL has reduced bioactivity & is present in 20% patients

'Hook effect'- Artefactual low PrL levels in cases of giant prolactinomas due to antibody saturation by high circulating PrL levels

Effects of Hyperprolactinemia

- Long standing hyperprolactinemia may result in hypogonadism, infertility, and galactorrhea, or it may remain asymptomatic.
- Bothersome Galactorrhea
- Bone loss occurs secondary to hyperprolactinemia-mediated sex steroid attenuation.
- Spinal bone density is decreased by approximately 25% in women with hyperprolactinemia and is not necessarily restored with normalization of prolactin levels

Symptoms of Hyperprolactinemia
- Oligo/ Amenorrhea (90%)
- Galactorrhea (80%)
- Infertility, PCOS
- Constant Headache
- Postmenopausal women with Headache, galactorrhea, visual field defect

Prolactin Levels
- PrL is a sensitive hormone with diurnal variation
- Sleep, exercise, breast stimulation, sexual intercourse & meals cause transient elevation
- Sample to be taken without excessive venipuncture stress preferably after adequate sleep

Elevated

Mild (30-60ng/mL) & **Moderate** (60-100ng/mL) Hyperprolactinemia

Severe Hyperprolactinemia (>100ng/mL)

Elevated TSH (>5mIU/L)

Treat Hypothyroidism Repeat TSH & PrL in 6-12 weeks

Galactorrhea Infertlity, PCOS

Medication related
Liver disease & Renal Insufficiency
Breast or chest wall surgery, cervical spine lesions,
Herpes zoster

Microadenoma(<1cm), Macroadenoma(>1cm)

Gadolinium Enhanced MRI Brain- extent of tumour, suprasellar extension & compression of optic chiasma
CECT in cases where MRI is unavailable/ contraindicated
Visual field examination-for macroadenomas abutting the optic chiasma

Management

Expectant Management
- May be self limiting
- Premenopausal with regular cycles
- Post menopausal – regular follow up
- Repeat PrL & scan in 3-6 months
- Drug Induced: Discontinue or replace medication

Medical Management
- Macroadenoma
- Microadenoma
- Infertility
- Bothersome Galactorrhea
- Long Standing Hypogonadism

Surgical Management
- Persistent visual field defect
- DA resistance/intolerance
- Unstable with neurological symptoms
- Trans-sphenoidal, endoscopic pituitary surgeries, transcranial surgeries

Bromocriptine
- Dose: 0.625-1.25mg daily, increase by 1.25 mg at weekly intervals
- Therapeutic Dose Range: 2.5-15 mg/day in divided doses
- Short half life
- S/E: Nausea, vomiting, headache, postural hypotension

Cabergoline
- Dose: 0.25-0.5mg once/twice weekly
- more potent, less side effects, longer action
- not licensed for early pregnancy

Adjuvant Therapy
- Calcium and Vit D
- Combined Oral Contraceptive Pills
- Ovulation Induction Drugs

Follow up
- Treatment with dopamine agonists is very effective for patients with prolactinomas and symptomatic idiopathic hyperprolactinemia
- Minimal duration of DA therapy is one year
- DA can be withdrawn after long term normalization of PRL levels for three years
- Hyperprolactinemia may recur after DA withdrawal in considerable no. of patients
- Success rates are higher in patients treated for idiopathic hyperprolactinemia, after treatment with cabergoline, and in patients with treatment duration of more than 2 years.

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Selective Estrogen / Progesterone Receptor Modulators: SERMs and SPRMs

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Selective Estrogen Receptor Modulators (SERMs)

SERMs are a class of synthetic non-steroidal agents with tissue-selective estrogen agonist or antagonist actions. These include:

Triphenylethylene derivatives	:	Tamoxifen, Toremifene, Ospemifene, Clomiphene
Benzothiophene derivative	:	Raloxifene
Indole derivative	:	Bazedoxifene
Benzopyrans	:	Ormeloxifene

Of these, tamoxifen, toremifene are 1st generation; raloxifene is 2nd generation and bazedoxifene, ospemifene, lasofoxifene are newer 3rd generation SERMs. Newer SERMs are molecules with potentially greater efficacy and potency than previous SERMs, and comparable efficacy to conventional hormone replacement therapy in animal models, with an improved safety profile. Many SERMs have been discontinued after making it to phase 3 clinical testing (droloxifene, idoxifene, levormeloxifene, arzoxifene). Ormeloxifene (Centchroman) is an indigenous SERM, developed by Central Drug Research Institute, Lucknow, India and has potent antiestrogenic, weak estrogenic and antiprogestational activities.

Molecular Mechanism of action

SERMs are structurally heterogenous estrogen receptor (ER) ligands that interact with intracellular estrogen receptors. Each SERM has the ability to induce distinct structural or conformational changes in the receptor; thereby influencing the receptors ability to interact with coactivators (CoA) or corepressors (CoR) and hence subsequently effect target gene transcription. The resulting biologic action varies according to the type of ER (alpha or beta; e.g. bone has both types of ERs while uterus has predominately ER alpha), cell or tissue, shape of the ligands, cofactors, responses and ligands leading to tissue specific agonist or antagonist or mixed activity. A high ER α:ER β ratio correlates well with high levels of cellular proliferation whereas the predominance of functional ER β over ER α correlates with repression of proliferation. Antagonistic action of certain SERMs may also be through competitive inhibition of estrogen binding to ERs.

Effect of SERMs on various tissues:

Effect on bones: In general, SERMs provide protection against menopausal bone loss due to estrogen agonist activity, although their effect on bone mineral density is lesser when compared with estrogen replacement. Reduction in fracture risk appears greater and out of proportion to their modest effect improving bone density, suggesting their additional benefits on bone microarchitecture.

Effect on Breast: Most SERMs have antagonistic action on breast. The approvals for tamoxifen use include treatment of metastatic breast cancer, adjuvant with chemotherapy, adjuvant therapy alone, treatment of ductal carcinoma in situ, risk reduction in high risk pre- and postmenopausal women and breast cancer treatment in men.

Effect on endometrium: A key differentiator amongst SERMs has been their variable estrogen effect at endometrium, varying from an agonist effect seen with tamoxifen, to neutral with raloxifene, to strong antagonist with bazedoxefine.

Effect on vagina: In general, SERMs have inconsistent effects on the vagina. Tamoxifen, raloxifene and bazedoxefine have no direct positive effects on the vagina. Ospemifene and lasofoxifene improve vulvovaginal atrophy and may be an alternative to vaginal or systemic estrogen therapy for symptomatic postmenopausal women.

Effect on cardiovascular system: Although raloxifene lowers circulating cholesterol in postmenopausal women, raloxifene does not reduce the risk of CHD in women at high risk. It rather increases risk of fatal stroke. Most other SERMs have not been found to alter cardiovascular events despite their positive effect on lowering total and low-density lipoprotein (LDL)-cholesterol concentrations.

Effect on central nervous system: These effects of SERMs on CNS are not well defined. SERMs may provide neuroprotection and even reduction of neural damage in neural trauma, brain inflammation, cognitive impairment, neurodegenerative disorders and mood disorders. SERMs may promote interaction of ERs with neuroprotective growth factors. Also reduced mRNA levels of proinflammatory molecules may counteract brain inflammation in neurodegenerative disease, which is found more with raloxifene and ospemifene than tamoxifen and bazedoxifene. Effects of SERMs on cognition are not clear.

SERMs as a class have shown an estrogen antagonist effect with a mild increase in hot flashes, generally not significant enough to discontinue therapy. The combination of a SERM and estrogen might relieve hot flashes.

Ideal SERM

The primary objective for the pharmacological development of SERMs is to increase the benefit/risk ratio in comparison with estrogen and estrogen/progesterone therapy in the postmenopausal period that are related to this physiological estrogen deficient state.

An ideal SERM would provide desirable estrogen agonist activity in bone (to prevent bone loss), brain, cardiovascular system and serum lipids, vagina, urogenital system and skin while providing neutral or antagonist effects in breast, endometrium to reduce cancer risks, and on risk of venous thrombosis with none of the adverse effects associated with current therapies. To date, no SERM provides the tissue specific actions desired to be ideal. Different SERMs provide different tissue specific actions allowing for individualization depending on the medical needs of the postmenopausal women.

Raloxifene would be the first SERM to be approved for two of the three properties of the "ideal SERM"- reduction in the incidence of fractures from osteoporosis and the reduction in the incidence of breast cancer.

Clinical applications of SERMs

Postmenopausal Osteoporosis: Raloxifene is the only SERM approved for the prevention and treatment of postmenopausal osteoporosis and vertebral fractures.

Other Postmenopausal symptoms: for menopausal vaginal changes and associated dyspareunia.

Breast Cancer: Most SERMs have antagonistic action on breast. Tamoxifen is the pioneering SERM which has evolved as the standard of care for the long term adjuvant therapy of ER positive breast cancer. Tamoxifen is used to treat all stages of breast cancer, metastatic breast cancer in postmenopausal women, chemoprevention in women at high risk for breast cancer and also has beneficial effects on bone mineral density and serum lipids in postmenopausal women. The approvals for tamoxifen use include treatment of metastatic breast cancer, adjuvant with chemotherapy, adjuvant therapy alone, treatment of ductal carcinoma in situ, risk reduction in high risk pre- and postmenopausal women and breast cancer treatment in men.

Infertility: Clomiphene citrate is used for premenopausal women with infertility.

Contraception: Ormeloxifene is recently added in the National Family Planning Programme as 'CHHAYA' as an oral contraceptive. Its contraceptive dose is 30 mg taken twice weekly or the first three months and then weekly thereafter. Ormeloxifene increases zygote transport through tubes, accelerates blastocyst formation and suppresses endometrial proliferation and decidualization; hence causes asynchrony between developing zygote and endometrial maturation leading to prevention of implantation. Since there is no disturbance of the endocrine system, normal ovulatory cycle is maintained. Being non-hormonal, it does not cause the nausea, dizziness, weight gain and other side effects associated with COCs. The contraceptive effect is readily reversible. The dosage simplicity ensures compliance with ormeloxifene. Ormeloxifene should be avoided in polycystic ovarian disease, cervical hyperplasia, jaundice or liver disease.

Abnormal uterine bleeding**:** Ormeloxifene is an effective option for medical treatment of AUB especially in patients who prefer nonsteroidal treatment, want contraception and in whom steroidal treatment is not recommended.

The prescribed dose for AUB is double that for contraception i.e. 60 mg twice/week for three months and weekly thereafter.

Breast Fibroadenoma: Ormeoxifene is used for treatment of breast fibroadenoma.

Adverse effects of SERMs

Hot flashes: Up to 45% of tamoxifene treated patients experience hot flashes, which can be treated with Venlafaxine, a Serotonin Norepinephrine Reuptake inhibitor. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine impairs the efficacy of tamoxifen as an anticancer agent has should not be used to treat hot flashes in patients taking tamoxifen.

Thromboembolic disorders: SERMs have an increased risk of venous thromboembolism (VTE) similar to estrogens. Raloxifene increases risk of fatal stroke. These adverse effects represent a major concern given that long-term therapy is required to prevent osteoporosis or prevent and treat breast cancer.

Amenorrhea: is reported in upto 40% patients with 60mg weekly ormeloxifene and upto 10% users may have delayed periods with contraceptive dose usually in the first three months of use.

Other adverse effects of ormeloxifene: Ovarian cyst in 15%, cervical erosion and discharge in 7%, gastric dyspepsia, vague abdominal pain and headache in about 5% cases is reported with 60 mg dose. Increased thickness on ultrasound may be seen in upto 9% cases.

Tissue-selective estrogen receptor complex (TSEC)

TSEC is a **new class** of drug combination, which combines a SERM and an estrogen. Different conformational changes in the ER receptors may occur with different SERM/estrogen combinations resulting in varying estrogen agonist /antagonist action. Determining whether a SERM can be paired with a systemic or

vaginal estrogen depends on how strong the estrogen antagonist effect is on the uterus. SERMs with stronger estrogen antagonist effects on the endometrium would be expected to have less risk of stimulating estrogen sensitive endometrial cancer if used either alone or in combination with vaginal or systemic estrogens.

So far, only one TSEC i.e. bazedoxifene (with a strong estrogen antagonistic action on uterus) and conjugated equine estrogens (CEE) combination has a proven safe and effective profile that relieves postmenopausal hot flashes and vaginal atrophy and prevents bone loss without stimulating breast or uterus. It also allows for the estrogenic benefits on relief of hot flashes. Bazedoxifene is significantly antiproliferative on the uterus, which obviates the need for concomitant progestogen use with estrogen.

Selective Progesterone Receptor Modulators (SPRMs)

SPRMs are relatively new class of non-steroidal progesterone receptor ligands which induce tissue effects ranging from pure agonists to agonist/antagonist to antagonist. Each SPRM has different affinity for progesterone receptor & varying degrees of antagonistic activity. Final action depends on interaction with coactivators and co-receptors in specific cell types. Mifepristone and Ulipristal acetate are the 2 SPRMs that are commonly used.

Mifepristone is the pioneer member of this class, discovered in 1980, which has antagonist action on progesterone receptors. Other SPRMs are Asoprisnil, Telapristone acetate, Onapristone, Lonaprisal, Vilaprisan. Ulipristal Acetate (UPA) is the most recent one being evaluated. To date, only mifepristone and UPA are licensed for clinical use outside clinical trials.

Mechanism of action

- Midluteal phase administration of UPA causes luteolytic activity and a dose-dependent antiprogestin effect on the endometrium. This attributes contraceptive (ie prevention of fertilisation) and contragestive (ie prevention of implantation) characteristics to UPA.
- Mifepristone owing to its predominant progesterone antagonist effect, has been used for medical abortions.
- As a progesterone antagonist, SPRMs acts as a proapoptotic or antiproliferative on leiomyoma cells without affecting normal myometrium. They also down-regulates expression of angiogenic growth factors decreasing neovascularization, hence reducing leiomyoma cell proliferation. UPA also increases the expression of matrix metalloproteinases and decreases the expression of tissue inhibitor of metalloproteinases and collagens in fibroid cells impairing tissue integrity.
- SPRMs also act on uterine endometrium decreasing bleeding symptoms
- Discrepancy b/w differential change in uterine/ fibroid volume but universal improvements in bleeding symptoms suggests that SPRM mechanisms underpinning control of bleeding may be independent of fibroid shrinkage

Clinical Applications of SPRMs are

- Leiomyoma and associated abnormal uterine bleeding and bulk symptoms
- Endometriosis
- Contraception
- Termination of pregnancy

SPRMs in Uterine fibroids

SPRMs are effective medical treatment option for abnormal uterine bleeding as well as for bulk symptoms associated with fibroids. Recent studies with UPA have caused a change of paradigm in the treatment of fibroids - not only for the preoperative treatment of moderate to severe fibroid-associated symptoms, but also, for long-term medical management as intermittent courses. Recently, two optimized algorithms have been proposed in 2017 for women in reproductive age with desire to preserve reproductive capacity and the other for >40 years with no desire for pregnancy.

Role of Mifepristone in uterine fibroids evaluated in a meta-analysis concluded that mifepristone given in the dose of 2.5 -25 mg/day, for a duration varying from 3-6 months causes ssignificant reduction in uterine & leiomyoma volume, alleviation of leiomyoma related symptoms with no added risk of atypical endometrial hyperplasia. Furthermore, after treatment cessation, menstruation usually started within 4–5 weeks.

Ulipristal Acetate (UPA) efficacy and safety has been evaluated in four phase III clinical trials (Pearl I, II, III, IV Trials) in which Pearl III and IV evaluated potential for long term management with intermittent treatment courses. At the end of the first UPA treatment course, 78.5% of women became amenorrhoeic, increasing to 90% after four courses, with a median time to amenorrhea of 2–4 days in each course. Heavy menstrual bleeding was controlled with pictorial blood loss assessment chart score of <75) in 90-98% patients. Amenorrhea developed in 70-90% patients. This control of bleeding was achieved within 7 days in 75.9% patients on 5mg and in 82.7% on 10 mg dose. Total fibroid volume reduced by 12-21% in Pearl-I and by 40-70% in volume of 3 largest fibroids in Pearl-II,III,IV trials. Pain reduction occurred in 5-20%. In intermittent courses, there was a cumulative decrease in fibroid volume. PAEC was reported in 57-62% cases. Menstruation usually started within 4–5 weeks of discontinuation, but volume reduction is sustained for up to 6 months.

Cochrane meta-analysis evaluating mifepristone, UPA and asoprisnil in premenopausal women with fibroids

concluded that SPRMs improved symptom severity, health-related quality of life without increasing endometrial hyperplasia.

SPRMs for medical management of endometriosis

Selective inhibition of endometrial growth without the side effects of hypoestrogenism, decreased menstrual bleeding by effect on the endometrial blood supply and suppression of endometrial blood supply are some of the mechanisms that have provoked interest in use of SPRMs for endometriosis.

Treatment with Mifepristone 50 mg daily, Onapristone and UPA has been shown to result in atrophy of the endometrium and suppression of estrogen- dependent endometrial growth. Decreased expression of COX-2 has also been shown with mifepristone and UPA. Studies are however limited.

Mifepristone for medical termination of pregnancy

Mifepristone owing to its predominant progesterone antagonist effect, has been used for medical abortions.

Ulipristal acetate for emergency contraception: UPA 30 mg is recommended for women, within 120 hours of unprotected intercourse. Women with repeated unprotected intercourse in the same cycle and obese women have a higher risk of unwanted pregnancy, and women who presented with both risk factors, had the highest rate of pregnancy (8.3% CI: 0.2–38.5%).

Adverse effects of SPRMs

- Hot flushes: in upto 10% (Moderate to severe) compared with 40% with GnRH
- Leg cramps, headache, nausea, vomiting, abdominal pain
- **Progesterone receptor modulators associated endometrial changes (PAEC):** SPRMs induces endometrial changes which are benign, reversible are now termed 'PRM associated endometrial changes.' These may contribute to inducing amenorrhea. A SPRM treated endometrium shows altered architectural glandular features, including cystic dilatation even though this glandular epithelium is inactive or contains few mitoses or apoptosis. Abnormal stromal vessels are commonly observed.

  Despite paucity of mitoses, PAEC may be mistaken for endometrial hyperplasia. Hence, pathologists must be made aware of the use of SPRM so that the possible histological changes induced by them are not misdiagnosed as endometrial hyperplasia or polyps.

  Treatment duration and cumulative dose do not affect occurrence of PAEC during intermittent UPA administration. Repeated courses of UPA did not increase the frequency of PAEC, reaching 16.2% and 10.3% after a fourth treatment course with 5 and 10 mg UPA in PEARL IV trial. The changes are rapidly reversible in most women within three months.

Currently FDA approved SERMs / TSEC / SPRMs for various indications are as follows

- Prevention and treatment of osteoporosis: Raloxifene, TSEC bazedoxifene/CEE (only for prevention)
- Prevention and treatment of breast cancer: Tamoxifen, Toremifene, Raloxifene
- Postmenopausal vaginal atrophy/dyspareunia: Ospemifene
- Treatment of hot flashes: TSEC bazedoxifene/CEE
- Emergency contraception: Ulipristal acetate
- Medical termination of pregnancy: Mifepristone
- Medical management of uterine leiomyomas: Ulipristal acetate (approved only in Europe, Canada, Australia)

Recently included in National Family Planning programme as oral contraceptive: Ormeloxifene (Chhaya)

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Management of AUB (COEIN)

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Introduction

AUB is reported to occur in 9 to 14% women between menarche and menopause. Prevalence of AUB is around 17.9% in India. To standardize nomenclature of AUB, a system known by the acronym PALM-COEIN (**P**olyp; **A**denomyosis; **L**eiomyoma; **M**alignancy and **H**yperplasia; **C**oagulopathy; **O**vulatory Disorders; **E**ndometrial factors; **I**atrogenic; and **N**ot classified) was introduced in 2011 by the International Federation of Gynecology and Obstetrics (FIGO). The PALM-COEIN system is etio-pathogenesis based, with PALM describing structural causes that can be measured visually with imaging techniques &/or histopathology and COEIN denoting non- structural causes of AUB that are not defined by imaging or histopathology.

COEIN

Coagulopathy (AUB-C)

- Approximately 13% of women with heavy menstrual bleeding have systemic disorder of hemostasis.
- Coagulopathy represents both inherited and acquired disorders, most common is inherited von Willebrand disease.

Ovulatory dysfunction (AUB-O)

- Can lead to amenorrhea or heavy menstrual bleeding.

Endometrial (AUB-E)

- Likely to occur when other abnormalities are excluded in the presence of normal ovulatory function.

Iatrogenic (AUB-I)

- Breakthrough bleeding during use of single or combined gonadal steroid therapy, intrauterine systems, or devices.
- Systemic agents that interfere with dopamine metabolism, or anticoagulant drugs.

Not classified (AUB-N)

- Rare or ill-defined conditions: Chronic endometritis, arteriovenous malformations, and myometrial hypertrophy.

Guidelines for investigation

General assessment

Women with both acute & chronic AUB should be evaluated for anemia with an assay of hemoglobin and/or hematocrit. Once the bleeding has been confirmed or, in the absence of any other identifiable source, suspected to be, of uterine origin, the clinician would proceed in a systematic fashion, designing the assessment to address each of the components of the classification system.

Determination of ovulatory status

Bleeding associated with AUB-O is typically irregular in timing & flow. Measurement of serum progesterone or timed endometrial biopsy may provide evidence of ovulation in case of uncertainty.

Screening for systemic disorder of hemostasis

Positive screen comprises any of the following:

- Heavy menstrual bleeding since menarche
- History of one of the following:
  - Postpartum hemorrhage
  - Surgical related bleeding
  - Bleeding associated with dental work
- Two or more of following symptoms
  - Bruising 1-2 times per month
  - Epistaxis 1-2 times per month
  - Frequent gum bleeding
  - Family history of bleeding symptoms

Evaluation of the endometrium

Endometrial tissue sampling is recommended in AUB:

- In women>40 years
- In women< 40 years who have high risk factors for carcinoma endometrium:
  irregular bleeding, obesity associated with hypertension, PCOS, diabetes, endometrial thickness>12mm, family history of malignancy of ovary/breast/endometrium/colon, use of tamoxifen for HRT or breast cancer, late menopause, HNPCC

Management

AUB-C (Coagulopathy)

- In patients with AUB-C, non-hormonal treatment with tranexamic acid (1-3 gm daily) as primary option and hormonal treatment with COCs/LNG-IUS as secondary option are recommended in consultation with haematologist, with the following considerations
  - For patients with uncontrolled uterine bleeding with above medical management, specific factor replacement where possible or desmopressin in refractory cases to be given.

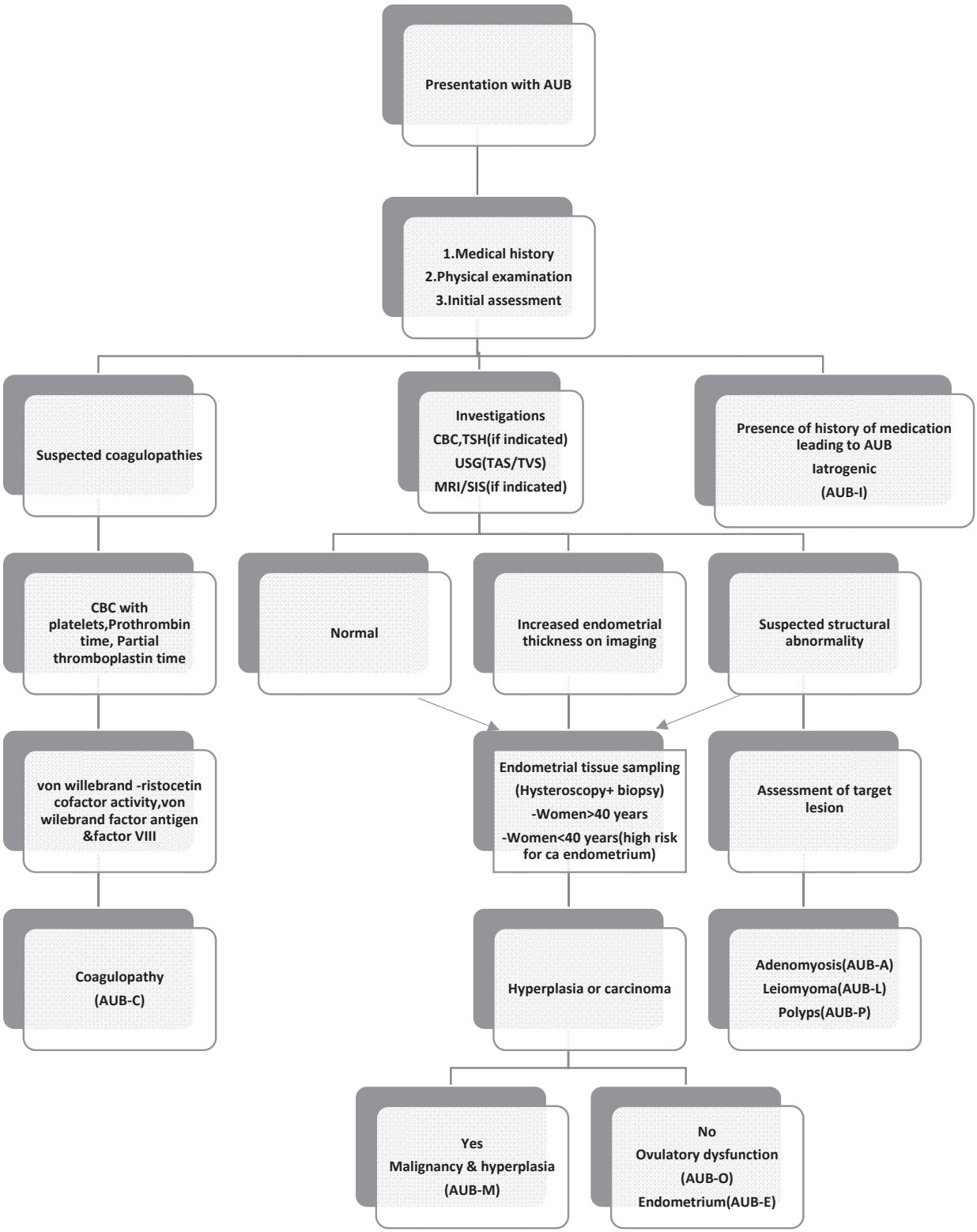

Figure: Algorithm for the diagnosis of AUB

- When surgical interventions are indicated, for appropriate pre-, intra- and post-operative management of bleeding.

NSAIDs & injectables (GnRH agonists) are contraindicated as they can alter platelet function and interfere with production of clotting factors.

AUB-O (Ovulatory Dysfunction)

- Combined oral contraceptive pills can be used for 6-12 months as first-line therapy in women not desiring conception.
- Cyclic luteal-phase progestins should not be used as a specific treatment in women withAUB-O.

- Norethisterone cyclically (for 21 days) is given as initial therapy in acute episodes of bleeding for short-term management of 3 months .
- Response is assessed after 1 year of medical management and if there is failure of medical management then surgical intervention is recommended.
- If COCs are contraindicated or patient is unwilling for COCs, LNG-IUS is recommended if she wishes to use it for atleast 1 year.
- Both hormonal and non-hormonal therapies can be prescribed in adolescents with AUB-O.

AUB-E (Endometrial)

Management of AUB-E can be similar to the management of AUB-O.

AUB-I (Iatrogenic causes)

Medications causing AUB should be changed to other alternatives, if noalternatives are available, LNG-IUS is recommended.

AUB-N (Not defined)

- LNG-IUS isrecommended as first-line therapy to reduce menstrual bleeding in women who desire contraception.
- Combined oral contraceptives are prescribed for women in whom, LNG-IUS is contraindicated.
- For the management of abnormal uterine bleeding that are mainly cyclic or predictable in timing, non-hormonal options such as NSAIDs and tranexamic acid are recommended.
- When medical or conservative surgical treatments (such as ablation) have failed or are contraindicated, GnRH agonists along with add-back hormone therapy are recommended to reduce idiopathic AUB, while hysterectomy is suggested as last resort.
- Uterine Artery embolization is recommended for A-V malformations

AUB-COEIN: General management guidelines

- Tranexamic acid is first-line therapy. Other non-hormonal option is NSAIDs except in AUB-C.
- In women desiring effective contraception, LNG-IUS is recommended.
- COCs are recommended as second line therapy in patients desiring effective contraception, but unwilling or unsuitable for LNG-IUS.
- Cyclic oral progestins (from day 5 to 26), are recommended if COCs are contraindicated.
- Centchroman is an option when steroidal hormones and other medical options are not suitable .
- Use of cyclic luteal-phase progestins are not recommended for AUB.
- GnRH agonists with add-back hormone therapy are recommended as a last resort when medical or surgical treatments for AUB have failed or are contraindicated.
- Role of conservative surgery such as ablation has decreased a lot due to availability of LNG IUS which works like medical ablation.

Suggested Readings

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- Shankar M, Lee CA, Sabin CA, Economides DL, Kadir RA, von Willebrand disease in women with menorrhagia: a systemic review, BJOG 2004;111(7):734-40.
- American College of Obstetricians and Gynecologists. ACOG committee opinion no.557: Management of acute abnormal uterine bleeding in nonpregnant reproductive aged women. Obstet Gynecol. 2013;121(4):891-6.
- Singh S, Best C, Dunn S, et al. Society of Obstetricians and Gynaecologists of Canada.Abnormal uterine bleeding in pre-menopausal women. J Obstet Gynaecol Can.2013;35:473-9.

Glimpses of 39th Annual Conference of Association of Obstetricians and Gynaecologists of Delhi 2017

Pre Conference Workshops - 17th November 2017

Evidence Based Fetal Care: Screening Protocols

Organizing Chairperson: **Dr Vatsla Dadhwal**
Organizing Secretary: **Dr K Aparna Sharma**

Pre-congress workshop on "Evidence based fetal care: screening protocols" was organized by "Fetal Medicine Subcommittee" at AIIMS, New Delhi on 17th November. The workshop was a huge success with 74 delegates and 26 faculty.

The focus was to take give a clear message about screening for aneuploidy in the first and second trimesters. The highlight was case based discussions, which was appreciated by the delegates. There was a talk on new tests in genetics, to help obstetricians understand the indications for these. This was followed by live demonstration of 2 cases of amniocentesis and chorionic villus sampling each. The delegates also got an opportunity for hands on practice of invasive prenatal diagnostic procedures on models.

Hands on Laparoscopy & Hysteroscopy Workshop

Organizing Chairperson: **Dr Malvika Sabharwal**
Organizing Secretary: **Dr Shivani Sabharwal**

AOGD organized a day long 39th Pre Congress endoscopic workshop, at Jeewan Mala Hospital on 17th Nov 2017 under the leadership of Dr. Malvika Sabharwal (President) & Dr. Shivani Sabharwal (Secretary). The organizers tried to put all their efforts to cover wide variety of topics.

Complication were dealt into and their management protocols were discussed in detail.

Endosuturing was covered in step by step manner. There were 10 active endotrainer stations for the delegates to get practical training.

Total of 21 delegates attended the workshop and enlightened themselves from the galaxy of 16 vibrant speakers who presented the subject precisely and made the day long session very interactive and informative.

Delegates were satisfied with lots of practical take home message and tips to incorporate into their day to day practices.

Infertility Workshop

Organizing Chairperson: **Dr Renu Misra**
Organizing Secretary: **Dr Priti A Dhamija**

Preconference Workshop on Infertility prior to 39th Annual Conference of AOGD was convened at Sitaram Bhartia Institute of Science and Research on 17th November 2017. There was a galaxy of very senior faculty. The program consisted of informative lectures and interactive panel discussions with good amount of audience participation. The hall was packed to capacity with more than half of delegates having done spot registration. In all we had 35 faculty and 56 delegates which included students and practitioners from Delhi and neighboring states.

In the second half, there was a live demonstration of sperm function tests and IUI with provision for hands on practice for delegates. Overall it was a highly successful workshop with an excellent program that made it a comprehensive session for delegates.

Intrapartum Skills Workshop

Organizing Chairperson: **Dr Abha Singh**
Organizing Secretary: **Dr Sharda Patra**

The department of Obstetrics & Gynecology organized a 'Workshop on Intra partum Skills as Pre congress AOGD workshop on 17th Nov 2017 in the Medical Education unit in SJ Auditorium, LHMC from 9.00am - 4.00pm.

Looking at some of the emergency situations faced by the obstetricians in the labor room an urgent need for enhancement of intra partum skills has become the need of the hour. The workshop on Intrapartum skills was aimed at enhancing the skills required in managing labor and the untoward complications associated with it. The workshop 's program was made diligently comprising of 3 symposia on most common intrapartum situations and a 2 hour hands on practice pertaining to postpartum hemorrhage and perineal tear repair. It was attended by quite a very good number of delegates 84 in number which included senior obstetricians, faculty, resident doctors, postgraduates plus some under graduates (n=10) and interns(11). The delegates were from various hospitals in and around Delhi including LHMC, AIIMS, Sir Gangaram hospital, MAMC, GTB Hospital, Jaipur golden hospital etc. The invited faculty including speakers and chairpersons of repute, who with their esteemed presence made the workshop a huge success. The talks given by the experts was very informative with videos and was very well appreciated by one and all. The interaction between the speakers and the delegates was also very informative. The Director LHMC Dr Rajiv Garg graced the occasion with his presence. This was followed by hands on practice on the simulators. There were three stations, one of Balloon tamponade for controlling PPH, then B lynch and uterine artery ligation and third one Complete perineal tear repair on pigs model. The delegates were divided in the different station and were allowed to practice in each station rotation wise. There was a continuous video running showing the technique of CPT repair, the delegates were first shown the videos followed by practice on the pigs model. There were 25 models of pigs perineal tissue. Each and everyone got an equal chance to practice these skills. It was also appreciated a lot. by all Altogether the workshop was very informative, interactive and was a huge success.

Gynae Oncosurgery Video Workshop

Organizing Chairperson: **Dr Rupinder Sekhon**
Organizing Secretary: **Dr Amita Naithani**

AOGD precongress workshop on Gyne Oncology: Surgical Videos was held on 17th November 2017 at Hotel Crowne Plaza Rohini

The organising chairperson was Dr Rupinder Sekhon, Head Gyne Oncology Rajiv Gandhi Cancer Centre and chairperson AOGD Oncology committee Organising secretary was Dr Amita Naithani. The workshop was a huge success and was attended by 118 faculty and delegates. International faculty Dr Mario Letao although was unable to attend but his surgical videos were presented.

Dr Anupama Director Robotic Surgery in Gynae Oncology, Amrita Inst of Medical Sciences, Dr SK Giri Director Gynae Oncology RCC Cuttack, Dr Amita Maheshwari Professor Gynae Oncology TMH Mumbai, Dr Neerja Bhatla Professor Gynae Oncology AIIMS, among others showed some beautiful surgical videos on pelvic anatomy and pelvic surgery. Overall the workshop was a huge success

Urogynaecology Precongress Workshop

Organizing Chairperson: **Dr Rajesh Ahlawat**
Organizing Secretary: **Dr Amita Jain**

On Friday 17th November, 2017, Fortis Kidney & Urology Institute organised 39th AOGD Pre-Conference Workshop and CME on "Urogynaecology" at Suryaa Hotel, New Friends Colony, New Delhi. The workshop was accredited with 7 DMC credit hours.

This was aimed to refine the knowledge & skills of managing female pelvic floor disorders, covering both theoretical and practical aspects.

The didactic lectures on burning subjects of urogynaecology by renowned experts like Dr Sanjay Sinha from Apollo Hyderabad, Dr Sanjay Pandey from Kokila Ben Mumbai, Dr Pawan Vasudeva and Dr Aparna Hegde from Delhi provided an excellent educational opportunity for the audience.

The detailed discussion after each talk provided an opportunity to further unfold the saga of knowledge and solve the queries of delegates.

To uphold interest and promote interaction with audience a short quiz was organised after each session. The attendees took active participation and won prizes as well.

The Panel discussions covering two important subjects of field of urogynaecology ie. Stress Urinary Incontinence and Prolapse, were designed to provide an assistance in understanding the rationale of various reconstructive procedures and applying this to clinical practice. Both panels were proceeded by detailed description of applied anatomy and followed by video demonstration of steps of all important procedures. This approach provided a complete understanding of the subject in systemic way.

Total 31 faculty and 41 delegates attended the workshop and got benefited.

Conference - 18th & 19th November 2017

39th Annual conference of AOGD, 2017 was successfully organized by Department of Obstetrics & Gynecology, UCMS & GTB Hospital on 18th & 19th November 2017 at India Habitat Centre, Lodhi Road, New Delhi.

The conference saw an overwhelming response with about 750 delegates and faculty. It was an educational extravaganza of Lectures, Panel discussions, Debates and Video presentations of cutting edge procedures.

The guest lectures by international and national experts, covered variety of important areas in the field of Obstetrics & Gynaecology. International faculty **Dr Soma Mukherjee**, **Head of Fetal Medicine unit, University of Warwick,UK** highlighted the role of SFLT-1/ PIGF ratio as predictors of pre-ecclampsia. Brigadier khanna oration was delivered by **Dr Mario M. Leitao Jr., Director Robotic Surgery at Memorial Sloan Kettering Hospital, New York** who presented the MSKCC data for management of endometrial cancer. Key note address on ABC of Breast Health by **Dr P. Raghuram, President Breast Surgeons Association of India** was very informative.

AOGD for the first time instituted **"Lifetime Achievement Awards"** which ware conferred at the inaugural ceremony on Dr S.N. Mukherjee and Dr Urmil Sharma for their immense contribution to the Association. The award consisted of a Plaque, Shawl and Scroll of Honour. Our patrons Dr Kamal Buckshee & Dr Neera Agarwal were also felicitated for their guidance & contributions in the field of Obstetrics & Gynecology.

The **Inauguration ceremony** was enjoyed by all and started with a skit on "Violence against Doctors" presented by UCMS students drama Society Manchayan. The ceremony was graced by Chief guest Dr Jagdish Prasad DGHS and Guest of Honour Dr Sunil Kumar MD GTB Hospital; who released the "**Conference Proceedings book"** and the book on **"AOGD Good Clinical Practice Guidelines".** This book was made possible by contribution of all AOGD sub-committees and their chairpersons were also felicitated.

The conference also saw keen competition amongst researchers and we received 125 papers and case reports with 21 current papers vying for prize of best competition paper. In all there were 45 oral presentations and rest e- posters presentation. The quiz on Obstetric Emergencies was also keenly fought.

There was good participation of pharmaceuticals with delegates enjoying information, games and the gifts. We were also fortunate in having excellent weather with balmy sunshine making the lawns of India Habitat Centre idyllic. The cuisine was also highly appreciated. The delegates went back with happy memories.




National & International Faculty

750 Delegates

Lifetime Achievement Awards Recipients
Dr S.N. Mukherjee & Dr Urmil Sharma

Dr S.N. Mukherjee Rotating Trophy
Winner – UCMS & GTB Hospital

Release of "Conference Proceedings"
& "Safe Practice Guidelines Book"

Felicitation of AOGD Sub – Committee
Chairpersons

Valedictory Function: Faculty with Prize Winners

Events Held in October 2017

AOGD Monthly Clinical Meeting at Auditorium, G - Block, 5th Floor, Hindu Rao Hospital on **29th September 2017**

AOGD Monthly Clinical Meeting

Cervical Cancer Awareness, Screening & Vaccination Drive Conducted

Cervical Cancer Awareness, Screening & Vaccination Drive Conducted on **5th October 2017** by OKTI Foundation and ONGC under aegis of AOGIN India & AOGD. The drive was helmed by Dr Sonal Bathla & Dr Priti Arora

AOGD Monthly Clinical Meeting at Auditorium, G - Block, 5th Floor, Hindu Rao Hospital on **29th September 2017**

Fertility Update


Post AGOICON "Master Class"

Post AGOICON "Master Class" was organized by Department of Obstetrics and Gynaecology AIIMS, New Delhi, on **30th Octber, 2017** from 2.00-4.00 pm under the aegis of FOGSI Oncology committee and AOGD Oncology committee under the stewardship of Dr Neerja Bhatla

FOGsd organized CME under aegis of AOGD on **Anaemia in Pregnancy and Current concepts of Genital TB** by Dr. JB Sharma on **31st October** at Grills and Platters under the able guidance of Dr. Anita Sabharwal.




Events Held in November 2017



AOGD Monthly Clinical Meeting

AOGD Monthly Clinical Meeting at Silver Jubliee Auditorium, ESI Model Hospital, Basaidarapur on 1st November 2017

Delhi PG Forum

Delhi PG Forum under the aegis of AOGD was organized on **07th November** at AIIMS under the guidance of Dr Alka Kriplani & Dr J.B. Sharma. Prof. Ronald Jones from University of Auckland, New Zealand delivered a lecture on **"Newer Screening Methods for Cervical Cancer"**

Fertility Update

Safe Motherhood Committee of AOGD organized a CME on **'Too early or too small - An update on Low Birth weight baby'** at Hotel Lalit on **11th November, 2017** helmed by Dr Ashok Kumar

AOGD Monthly Clinical Meeting on Friday, **24th November, 2017** at Maulana Azad Medical College & Lok Nayak Hospital

AOGD Monthly Clinical Meeting

CME by FOGsd under aegis of AOGD

CME by FOGsd under aegis of AOGD on **30th November** at Sarover Portico, Nehru Place. The topics discussed were breast cancer update by Dr Ankur Behl & Vaccination in adolescent by Dr Sonia Naik

Appraisals and Accolades!!
Congratulations on the Success.....

"Team UCMS and GTB very well organised conference. Three cheers for the organisers"
- Dr Anjila Aneja

"Three cheers for Dr Shalini, Dr Abha & team UCMS & GTB for organising such an academic feast"
- Dr Veena Bhat

"Excellent sessions wonderful venue beautiful faculty"
- Dr Vanita Suri

"Lovely stoles and conference bags too! Thank you And most important 'Good Clinical Practice Guideline' "
- Dr Aruna Batra

"Good to honour our teachers. Good show Shalini congratulations to you and whole team"
- Dr Manju Khemani

"Excellent programs today! Congrats"
- Dr Shashi Prateek

"Enjoyed it! Thanks Shalini, Kiran and the whole team for the wonderful evening!"
- Dr Ranjana Sharma

"The faculty dinner rocked Shalini. Congratulations"
- **Dr Nirmala Agarwal**

"Excellent programme. Wonderful evening with songs and dinner. Congrats"
- Dr Ashima Taneja

"My heartiest congratulations for putting together an excellent scientific program and high quality deliberations. Thanks for wonderful hospitality."
- Dr Amita Maheshwari

"Congratulations Dr Shalini and whole GTB team for superb show proud of you all"
- Dr Kuldeep Jain

Thanks for the wonderful academic feast. Has been very helpful for my 'unlearn & relearn' program"
- Dr Ashwini Setya

"A true academic feast Congratulations to the entire team"
- Dr K Gujral

"Thanks Aogd team!! Fabulous effort"
- Dr Sushma Sinha

"Heartiest Congratulations to the organising team AOGD for such a wonderful academic feast n for all the hard work done. It was great to be a part of it."
- Dr Shelly

"Great Conference. Thanks for making me a part of it."
- Dr Puneeta

"Congrats, the conference was great, and very well attended. A special clap for u Shalini for connecting personally with everyone who participipated."
- Dr Gauri Gandhi

"Team Aogd and dept of obs and gynae GTB for a wonderful show."
- Dr Manju Puri

"Heartiest congratulations to team UCMS and GTBH for an excellent scientific conference and high quality deliberations."
- Dr Satinder Kaur

"Heartiest congratulations to AOGD, GTB team led by Dr Shalini for the excellent event. Full halls in Sunday evening at 5:00 pm."
- Dr Talwar

"Congratulations Dr Shalini & Dr Abha for organizing the Aogdbeautifully. Hard work, great choice of bags and stole. Thanks."
- Dr Alka Gujral

"Thank you AOGD for being a wonderful host. Enjoyed the scientific session 19/11/17, 6:47"
- Dr Kamini Rao

"It was truely a unique conference. Great academics. Everything to perfection including the warmth! Loved every moment."
- Dr Surveen

"Congratulations Shalini and the team on the great success of the conference! The stole was an excellent idea! Thanks"
- Dr Ranjana Sharma

"Excellent conferance n its a grand success. Each n everything very well thought n equally well executed..lots of hard work seen."
- Dr Shibani

"It was truely a fantastic conference. Great scientific sessions. Everything to perfection including the warmth and the gifts!"
- Pikee Saxena

"Congratulations whole GTB team for a super successful and very informative conference."
- Dr Rashmi Sharma

Congratulations to the entire team for such a well organized academic feast.
- Dr Urvashi

"Congrats Dr Shalini and team GTB. Great feat"
- Dr Gouri Devi

"Congrats on the great successful conference. Keep it up"
- Dr Raj

"Congratulations Shalini n the whole team thanx to u we felt involved in the conference n a part of it everything was very well organised!"
- Dr Somnath

"Congratulations Dr Shalini and team for the academic feast and superb arrangement"
- Dr Uma Rai

"Congrats for a wonderful conference with high standards and style, loved the warmth both hospitality as well one inside the bag."
- Dr Sweta Balani

"Wonderful organisation. The book on Guidelines will be ready reckoner in a busy practitioner's clinic."
- Dr Shakuntla Kumar

"Truly an academic feast par excellence.. enjoyed every bit of it... looking forward to winters now with ur beautiful gift."
- Dr Nidhi Khera

"Thanks to whole organizing committee of AOGD conference... for giving us latest guidelines for evidence based medicine...congratulations..."
- Dr Anita Rajorhia

"Thankyou very much for inviting me to be a part of your lovely conference Shalini. Great job. Kudos to you and your entire team."
- Dr Sasikala Kola

"Congratulations for successful conference and thanks for including me in this academic feast."
- Dr Aruna Nigam

"Dear shalini n aogd team...lovely conference, there was a sense of warmth comradarie n colour I felt yesterday. Congrats all of u. Great efforts for teaching."
- Dr Shylasree

"Thank you Shalini for an academic delight. Perfect flavour for an annual meet. Pleased to be a part of it. Great effort by your team and kudos to them too. Congratulations."
- Dr Ashok Khurana

"Congrats Drshalini and team aogd for a well organised enjoyable and fruitful conference. Feel proud of AOGD"
- Dr Chitra Raghunandan

"Kudos to dear Shalini, the great academician and the whole faculty for putting up this great show. My heart swelled with pride to see the energetic lovely young faculty going about all the responsibility, with poise and perfection."
- Dr Poonam

"Thanks for letting me be a part of this wonderful wonderful conference. Your hard work is admirable. Full halls"
- Dr K Gujral

"Congratulations team AOGD. Thanks for the warm hospitality and the exceptional scientific program.
- Dr Ratna

"The deluge of congratulatory messages is ample proof of how happy people were with the arrangements as well as the academic contents. Such a huge event needs meticulous planning and execution. Special kudos for the idea of lifetime achievement awards"
- Dr Sabhyata

"Very well said! All aspects well thought through and superbly an aged and executed! Congratulations to Shalini for superb leadership and to the entire team of GTB for their wholehearted efforts!"
- Dr Neerja Bhatla

"Thank you very much Shalini and team GTB for the wonderful conference. It was a great job.
- Dr Sonia Malik

"It is always a great sense of satisfaction and contentment and seated happiness after the completion of a very well organised and successful conference. You all deserve a huge applause and congratulations... Please enjoy every memory and appreciation as we enjoyed every moment of the conference."
- Dr Jyoti Bhaskar

Oral Ovulogens–Using Evidence Based Reviews in Management Decisions

Surveen Ghumman Sindhu
Director & Head, Dept of IVF & Reproductive Medicine, MAX Multispeciality Hospitals, Panchsheel, Saket, Patparganj & Vaishali

Oral ovulogens constitute the most commonly used intervention in a subfertile couple for ovulation induction (OI). They have the advantage over gonadotrophins of being of lower cost, safer and easy to administer. The main oral ovulogens utilised are Clomiphene and Letrozole. Insulin sensitizers may on their own also induce ovulation in PCOS women

Physiology of Ovulation

FSH promotes follicular growth because of 2 events,

1. ***FSH threshold***: The FSH threshold is the level of FSH below which no follicular growth can be initiated.
2. **FSH window**: The FSH window is the number of days that serum FSH levels are above the threshold and determines the number of follicles which are activated. Longer the window more the follicles recruited

   Since sensitivity of the follicle increases with development, the required FSH for a follicle will decrease. The balance between the decreasing levels of FSH and increasing FSH sensitivity is responsible for the growth of the follicle. All ovarian stimulation drugs raise the FSH levels by exogenous FSH or increased secretion of endogenous FSH to reach the threshold and prolong the window in order to obtain specific number of follicles to be growing.

How do oral ovulogens cause folliculogenesis?

Clomiphene and tamoxiphene cause depletion of hypothalamic estrogen receptor (ER). This causes estrogen concentrations to be perceived as falsely low leading to a feedback to trigger normal compensatory mechanisms that stimulates increased secretion of FSH, in turn, serves to drive ovarian follicular activity once it is above the FSH threshold.

Letrozole blocks conversion of androgens into estrogens by aromatase inhibition thus, lowering estradiol levels. This, through the feedback mechanism to pituitary increases FSH, resulting in follicular growth once it is above a threshold levels. Since, the feedback mechanism is intact; normal follicular growth, selection of dominant follicle, and atresia of smaller growing follicle occurs, thereby facilitating monofollicular growth and preventing multiple pregnancy. Letrozole also increases intraovarian androgens thus making the follicle more sensitive to FSH.

Indications

Indications for use of oral ovulogens are women with WHO type II anovulatory infertility (majority being PCOS), unexplained infertility or in cases where IUI is being done for endometriosis to improve results by increasing follicles.

Prerequisites for ovulation induction

All important causes for infertility should be ruled out by a detailed history, examination and relevant tests of both partners. Baseline tests like semen analysis, a thyroid and prolactin evaluation, and blood sugar should be done. A day 2 ultrasound of pelvis is recommended. It gives an idea of the ovarian pathology like a basal cyst, assessment of PCOS, and antral follicle count for ovarian reserve. It also rules out tubal or uterine pathology which would affect outcome like hydrosalpinx, fibroid or polyp.

Who should be counseled for expected poor response?

Lower ovulation rates are seen in females with higher BMI, higher free androgen index, insulin resistance, large ovarian volume, older women, hyperandrogenic PCOS with severe cycle disorder.

CLOMIPHENE (CC)

Chemically, CC is a nonsteroidal triphenylethylene derivative and, like other such compounds (e.g., tamoxifen), exhibits both estrogen agonist and antagonist properties. It has an anti estrogenic effect on endometrium and cervical mucus which may cause a failure to achieve pregnancy.

Dosage: Usual starting dose is 50 mg/day for 5 days, from day 3 -5 of cycle, in women less than 50 kg. In women with weight more than 75 kg, 100 mg/day can be started. With 50mg/day 46-52 % patients ovulate, with 100 mg/day 21-22 % ovulate and with150 mg/day 8-12%[1]

Length of regime and when to start: Usually 5 days of clomiphene from cycle day 3 to 7 is given. Recent Cochrane

review 2016 stated that low-quality evidence suggested that a 10-day regimen of clomiphene citrate improves pregnancy rates compared with a 5-day regimen, but further research is required.[2] A thin endometrium due to impact of clomiphene may be avoided by starting the drug early on cycle day 2 so that effect does not persist beyond 7 days giving endometrium time to grow before follicle matures

Side effects: Common side effects of clomiphene include hot flashes, headaches, abdominal bloating and pain, nausea and vomiting, mood changes, and breast tenderness. Visual symptoms such as blurring, double vision, or seeing spots occur in 1 to 2 percent of women, and usually resolve when treatment stops.

Ultrasound monitoring – When should it be done?

Preferably, the first cycle of ovulation induction must be monitored by ultrasound to establish that there is no resistance to the drug and that no adverse effects like thin endometrium is there. Once follicle is 18-20 mm hCG can be given and rupture documented on ultrasound. Subsequent cycles may be unmonitored once efficacy of drug has been established. However, as good practice a baseline scan on day 2 is recommended before each cycle to rule out ovarian cyst which, may occur due to cumulative effect of clomiphene. Gap cycle is recommended because of this effect.

Number of cycles: Since most of the pregnancies occur in first 3-6 cycles, treatment beyond 6 cycles is not recommended. Failure to ovulate is termed as ***clomiphene resistance***. Failure to conceive despite ovulation with CC is termed as ***clomiphene failure***.

Why is the Miscarriage rate high with CC induction?

Clomiphene triggers the pituitary gland to secrete an increased amount of FSH and LH. High LH levels causing early resumption of meiosis, may be responsible for the high abortion rate of upto 23% in these conceptions. A high LH (>10IU/L) was found in 75% of women who aborted compared to 37% with an ongoing pregnancy.[3]

What optimal number of mature follicles should be aimed for and their impact on outcome?

In a meta-analysis of 11599 IUI cycles, during monofollicular growth the absolute pregnancy rate was 8.4% with 0.3 % multiple pregnancy. While after multifollicular growth the absolute pregnancy rate was 15 % with 2.8% multiple pregnancy rate. The OR for multiple pregnancies after two follicles was 1.7 (99% CI 0.8–3.6), and increased significantly for three and four follicles (2.8 and 2.3, respectively).[4] Hence, ideally one should aim for 2 follicles for a better pregnancy rate.

Which Adjuvants are useful with clomiphene?

The comparison of clomiphene citrate plus medical adjunct versus clomiphene alone (ketoconazole, bromocriptine, dexamethasone, combined oral contraceptive, human chorionic gonadotropin, hormone supplementation) was limited by the number of trials and poor reporting of clinical outcomes (Cochrane 2016)[2]

Dexamethasone the only effective adjuvant: Dexamethasone reduces circulating DHEAS, testosterone and LH levels. Additionally it may act directly on pituitary to suppress the action of estradiol. The addition of dexamethasone or combined oral contraceptive suggested a possible benefit in pregnancy outcomes specially in CC resistant cases. (Cochrane 2016).[2] It is usually given from day 5 to day 14

Tamoxifen

Tamoxifen is also a SERM with antiestrogenic action at hypothalamus but estrogenic action at endometrium and vagina, while its action on cervical mucosa is controversial. It is given 20-40 mg /day for 5 days. Starting dose is 20 mg/day and can be increased upto 40 mg/day for 5 days from day 3 of menstrual cycle.

Tamoxifen vs Clomiphene

Cochrane review (2016) states that between clomiphene and tamoxifen there was no clear evidence of a difference in the chance of a live birth (OR 1.24,), miscarriage (OR 1.81), clinical pregnancy (OR 1.30), multiple pregnancy or OHSS.[2]

Tamoxifen should be preferred if clomiphene cycle or monitoring in natural cycle has shown a thin endometrium.

Aromatase Inhibitors (AI)

Anastrazole and Letrozole are third generation aromatase inhibitors

The estradiol level per growing follicle is 40-60 % lesser in cycles where AI are utilized for ovulation induction or COS. This is in line with the reduced functioning of the intraovarian machinery responsible for converting androgens to estrogens.

Letrozole has advantages over clomiphene like

1. It does not deplete ERs throughout the body.
2. It keeps the hypothalamo-pituitary axis intact.
3. It is short acting (45 min half-life).
4. Better endometrial receptivity and blood flow favourable for implantation

Side effects: The main side effects when used for ovulation induction or superovulation include mild headache and muscle or joint pains. Letrozole works

based on its ability reduce estrogen levels leading to hot flashes, headaches, breast tenderness and menopausal symptoms like vaginal dryness and sexual dysfunction.

Dose: The usual dose of letrozole used is 2.5 or 5 mg and anastrozole 1 mg, both given for 5 days from day 2-3 of spontaneous or withdrawal bleed. Different doses of letrozole have been considered where in a study showed that a single dose of 20 mg letrozole may achieve a comparable pregnancy rate.[5] letrozole is approved for ovulation induction. Anastrozole has similar actions and outcomes as letrozole.

Individualizing use of Clomiphene and Letrozole According to Cause of Infertility

Unexplained infertility would require a drug which causes multifollicular growth whereas a PCOS patient may require a drug which causes a monofollicular growth. Hence the administration of oral ovulogens should be individualized according to need.

I. Unexplained Infertility – Which is the drug of choice?

Letrozole and clomiphene have been tried in unexplained infertility in many studies. Former at dosage between 2.5 – 7.5 mg/day while the latter at 100 mg/day dosage. A recent meta analysis showed equivalence in terms of pregnancy rate in between both ovulogens, though the number of growing follicles were lesser with letrozole.

Comparison of clomiphene, letrozole and anastrazole in unexplained infertility did not show superiority of any drug over the other.[6]

Achieving multifollicular growth with letrozole for cases of unexplained infertility.

Usually, multifollicular growth gives better results in unexplained infertility. There are regimes by which multifollicular growth can be achieved with letrozole although it is used more for its monofollicular growth advantage

1. **Extended letrozole therapy**
   Extended letrozole therapy for 10 days was tried in previously failed clomiphene citrate cycles. They were randomized to receive either 5 mg of letrozole for 5 days or 2.5mg for 10 days. With the same ovulation rates more follicles were seen in the extended regime with higher pregnancy rates (12.4% and 17.4%).[7]
2. **Using a higher dose of letrozole**
   On comparison of dose of 7.5 mg/day to as much as 12.5 mg/day, ovulation number was greater for increasing doses of the drug, while endometrial thickness was unaffected.[8]
3. **Adding Gonadotropins**
   AI with added gonadotrophins can be used if more than one follicle is required to be grown as in case of unexplained infertility.[9]

   Combined Gonadotropin and oral ovulogens in unexplained infertility

   For the management of unexplained infertility both clomiphene citrate and letrozole appear to be equally effective, but less effective than gonadotropin based treatments**.** Among patients who have been ovulatory but unsuccessful in conceiving by both clomiphene citrate and letrozole alone in IUI cycles, a combined OI/IUI induction cycle by letrozole/clomiphene and FSH is a reasonable and affordable alternative to patients who are otherwise unable to consider FSH-alone/ IUI or IVF due to financial or travel concerns.

   Protocol: Clomiphene or letrozole is started on day 3 for 5 days. Additional gonadotropin can be given on day 4 & Day 6. Alternatively gonadotropins can be started on day 8 and day 10 and continued as per requirement. Ultrasound monitoring is necessary to decide dose and days of gonadotropin supplementation

II. PCOS - Which is drug of choice?

Clomiphene vs Letrozole

In a recent Cochrane review, it was shown that letrozole when compared to clomiphene had significantly better live birth rate (OR 1.63) and clinical pregnancy rate (OR 1.32). The reviewers advised caution in interpreting the results as the quality of evidence was low.[10]

Letrozole is at least as effective, if not better than clomiphene in this group of women.

Clomiphene resistant PCOS – Which drug and dose?

The indication most widely studied for letrozole usage has been that of PCOS. Below are afew conclusive studies which help to guide in practical clinical management.

i. **Letrozole vs Placebo:** In clomiphene resistant PCOS, when compared with placebo, letrozole was shown to have 33.3 % ovulation rate compared with nil in the placebo group.[11]

ii. **Letrozole vs clomiphene in higher doses:** PCOS who failed to ovulate when taking 100 mg/d of CC in previous cycles on taking letrozole vs higher dose of clomiphene 150 mg had higher ovulation (62.5%vs37.50%) and pregnancy rate (40.62% vs 18.75%) with letrozole.[12]

Letrozole is preferred to using a higher dose of CC in CC resistance

iii. Letrozole step up protocol vs Gonadotropin cycle

In this regime letrozole was started at 2.5 mg and stepped up daily till 10 mg on fourth day. This in CC resistant PCOS lead to higher number of follicles 1.5 but still less than HMG cycle (3 follicles). However, pregnancy rates were comparable 16% vs 18% respectively, showing that better quality follicles were stimulated with letrozole leading to a higher pregnancy rate per follicle.[13] It is more cost effective than a gonadotropin cycle

Letrozole should be tried in CC resistant cases before using gonadotropins

A "stairstep" Protocol or The escalation protocol: It was performed by administering letrozole at a starting dose of 2.5 mg for 5 days starting cycle day 3. A transvaginal ultrasound was performed on cycle day 10-12 to assess follicular recruitment. If no follicle(s) >10mm were observed, the dose was immediately increased by 2.5 mg of letrozole for an additional 5 days. This was repeated until a follicle was recruited or a maximum dose of 7.5 mg of letrozole was reached. The escalation protocol increases ovulation rates in patients with PCOS by effectively identifying the letrozole dose necessary to achieve follicular recruitment during the initial ovulation induction cycle.[14] ***Increasing the dose of letrozole in a single cycle does not exhibit detrimental effects on the number of follicles recruited, endometrial development or pregnancy rates in CC resistant women***

iv. Letrozole vs Laparoscopic ovarian drilling

On comparing results of letrozole daily for 6 cycles with 6 months of follow-up of LOD, ovulation (65.4%vs 69.3%), pregnancy (15.6% vs 17.5%), miscarriage and live birth rates were similar between the two groups both being equally effective for inducing ovulation and achieving pregnancy in CC-resistant PCOS patients.[15]

Before surgical intervention with LOD letrozole induction must be tried as it has equivalent results in CC resistance

III. Normo responders and Poor responders - Should oral ovulogens be added to a gonadotropin cycle?

Addition of letrozole reduced gonadotropin dose required for COH in women who are normoresponders and improved ovarian response to FSH in poor responders as well.[16] This makes the regime more cost effective since the dose of rFSH required was significantly lower in the high letrozole dose regimen (5 mg vs 2.5 mg).

Letrozole has a beneficial effect in both normo and poor responders in a gonadotropin cycle

Congenital Anomalies and Oral Ovulogens

There were concerns about birth defect with letrozole due to which its use had been prohibited for many years. However many studies have shown it to be a safe drug and currently its use as an ovulogen is acceptable. There was no significant difference in the overall rate of congenital malformations among children born to mothers who conceived naturally or after letrozole or CC treatment.[17]

Success Rates with Oral Ovulogens

Ovulation rates with both clomiphene and letrozole are in the range of 70-80 % and pregnancy rate per cycle around 10-25 %.

Insulin Sensitizers

The major insulin sensitizers available include metformin and thiazolidinediones.

Metformin is an oral biguanide which reduces the peripheral insulin resistance, serum insulin and blood glucose levels. By improving insulin sensitivity, metformin reduces CYP17 activity in the ovary. It reduces androgens. The newer agents rosiglitazone and pioglitazone are category C drugs as per FDA due to their potential risk of causing fetal growth restriction in animal experiments.

Dosage: The usual dosage of metformin is 1.5 – 2 gm/ day in divided doses which is gradually stepped up. The start of metformin should be before ovulation induction in order to get the maximum effect of the medicine.

Side effects: The commonest side effects are related to the G.I tract and include diarrhea, cramps, nausea and vomiting. The most serious, but rare side effect is lactic acidosis.

There are various studies done to analyze when metformin should be added in cases where ovulation is being induced

1. **Should metformin be used as a first line therapy compared to a placebo or no treatment**?
   ASRM (2017) and a Cochrane (2017) reviews suggests that metformin alone may be beneficial over placebo for live birth, although the evidence quality was low.[18,19]
2. **Metformin monotherapy vs clomiphene**
   When metformin was compared with clomiphene citrate, an improvement in clinical pregnancy and ovulation with clomiphene suggests that ***clomiphene citrate remains preferable to metformin for ovulation induction*** in obese women with PCOS. (ASRM 2017)[18]
3. **Does adding Metformin to clomiphene improve results?**
   A higher ovulation and pregnancy rate was seen

as per a recent Cochrane review when combined therapy of clomiphene with metformin was given compared with clomiphene alone (OR 1.74 and 1.5 respectively). There was ***no evidence that combined therapy improved the overall live births*** compared with clomiphene alone.[20]

4. Does adding metformin to gonadotropins improve results?

Metformin plus FSH was associated with a ***higher cumulative live birth rate*** when compared with only FSH in PCOS women (OR 2.31) (Cochrane 2017).[21] It also shows a decrease in incidence of OHSS.

Currently, the only acceptable indication for metformin is impaired glycemic control and documented insulin resistance. There may be some role to play in obese CC resistant anovulatory women but evidence is mixed on clinical pregnancy rates. Live birth rates do not differ with metformin. The side effects like gastrointestinal side effects should be weighed against advantage of decreased OHSS.

To conclude, available data shows that letrozole and clomiphene are equally effective for ovulation and have comparable live birth rates. There is no difference in the birth defect rate compared to natural conception. Letrozole has a definite role in CC resistant PCOS. Many studies have shown letrozole to be as effective as gonadotropins and LOD, with added advantage of low cost and lower multiple pregnancy rates. Insulin sensitizers are useful where insulin resistance has been documented.

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Role of Dienogest in Gynecological Practice

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Structure

Dienogest, is structurally known as 17α-cyanomethyl-δ9-19-nortestosterone or as 17α-cyanomethylestra-4,9-dien-17β-ol-3-one. It is a member of the estrane subgroup of the 19-nortestosterone family of progestins. Unlike other 19-nortestosterone progestins, it is not a derivative of norethisterone (17α-ethynyl-19-nortestosterone) because it uniquely possesses a cyanomethyl group at the C17α position rather than the usual ethynyl group and has a double bond between the C9 and C10 positions[1,2].

Pharmacodynamics & mode of action

Dienogest, a 19-nortestosterone derivative progestin has antiandrogenic activity and is a progesterone receptor (PR) agonist. Though the drug has weak affinity for the PR it shows strong progestogenic effects on the endometrium[3,4]. The inhibition of ovulation by dienogest reportedly occurs mainly via peripheral action as opposed to central action on gonadotropin secretion producing hypoestrogenic environment; therefore, patients have reduced serum progesterone levels to anovulatory levels, however serum levels of luteinizing hormone and follicle-stimulating hormone are not significantly altered. Dienogest has no glucocorticoid, or antimineralocorticoid activity3. This molecule also demonstrates antiproliferative, anti-inflammatory and antiangiogenic effect.

Pharmacokinetics

Dienogest is rapidly absorbed and is exclusively protein-bound to albumin (only 10% being free) and does not bind to sex hormone-binding globulin or corticosteroid-binding globulin[3]. The drug is metabolized in the liver mainly by CYP3A4 hence dosage needs alteration in CYP3A4 inducers and inhibitors. In mild & moderate liver impairment the dosage need not be adjusted. However, in history of and current severe hepatic disorder, dienogest is contraindicated. No dosage adjustment necessary in renal impairment.

The terminal half-life of dienogest is 10 hours and reaches steady-state concentrations after 2 days of administration. Its metabolites are inactive and are rapidly excreted from body.

Uses in Gynaecology

1. Endometriosis

Endometriosis is a chronic condition affecting women in child bearing age. Nearly half of those who are affected have chronic pelvic pain, dyspareunia and dysmenorrhea.

Mechanism of action: Dienogest is a steroid with antiandrogen properties that lacks androgen, mineralocorticoid or glucocorticoid activity. Exhibits strong progestogenic effects although it binds uterine progesterone receptors with an affinity much lower (about one-tenth) than that of progesterone. Decreases estradiol production and thus suppresses estradiol's trophic effects on eutopic and ectopic endometrium. Inhibits cellular proliferation via direct antiproliferative, immunologic, and antiangiogenic effects.

Initiation of therapy: Pregnancy test prior to initiating therapy is essential; Papanicolaou smear, breast examination, mammogram; adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding; bone mineral density (prior to therapy in patients at risk for osteoporosis and as clinically indicated in adolescent females); assess for signs and symptoms of thromboembolic disorders, vision changes.

Clinical course during treatment: Patient is mostly relieved of pain. The menstrual cycles become irregular or cease altogether due to inhibition of ovulation. Return of menstrual cycles often occurs by 2 months.

Dose: This drug is usually given in a dose of 2 mg daily for 6 months. However, it has reportedly been used upto 16 months[5].

Long term benefits: Effective symptom control and predictable adverse effects significantly contributes to its high compliance. Pain relief in endometriosis is significant which may persist for 1-2 years even after stoppage of the drug.

Advantages over other medical therapies: Progestin-only treatment avoids the estrogen-related thromboembolic risk seen with estrogen-containing contraceptives. Compared with the GnRH agonists, high-dose oral progestin treatment is not associated with bone loss and is less expensive[6,7]. However long term treatment with dienogest may reduce bone mineral density and its use in adolescence should be used with great caution weighing the risk vs.benefit

2. Contraception

Used as progestin in multiphasic oral contraceptive pills. It is distributed under the brand name of Natazia (United States) and Qlaira (United Kingdom), no commercial brand is available in India.

Dosage: Pill consists of estradiol valerate (E_2) as estrogen and Dienogest (DNG) as progestogen. It aims of reducing total monthly hormone intake while maintaining the efficacy.

Table 1: Dosage in Contraceptive Pill Containing Dienogest

Day of the Cycle	Dosage
Day 1 to day 2	E_2 (3mg) + DNG (2mg)
Day 3 to day 8	E_2 (2mg) + DNG (2mg)
Day 9 to day 26	E_2(2mg) + DNG (3mg)
Day 27 to day 28	E_2(1mg) + DNG (3mg)

Long term benefits: This multiphasic pill provide the hormone delivery as per the natural menstrual cycle with fewer side effects like amenorrhea, breakthrough bleeding and decreased incidence of acne.

Advantages over other OCP's: It is associated with fewer spotting days, mean reduction in blood loss, reduced breakthrough bleeding, effective in heavy menstrual bleeding and stability in carbohydrate metabolism[8].

Drawbacks: Error in pill taking (multiphasic pill) and hence increased failure rates; Difficulty in postponing menstruation if required

Contraindications

1. Hypersensitivity to dienogest
2. Undiagnosed abnormal vaginal bleeding
3. Active venous thromboembolic disorder; history of or current arterial and cardiovascular disease
4. History of or current severe hepatic disease
5. Ocular lesions due to ophthalmic vascular disease, such as partial or complete vision loss or defect in visual fields
6. Current or history of migraine with focal aura
7. Breast-feeding; known or suspected pregnancy
8. Sex hormone dependent malignancy

Side effects

1. Central nervous system: Headache (7%), depression (3%), disturbed sleep (2%), irritability (1%), migraine (1%), nervousness (1%)
2. Dermatologic: Acne vulgaris (2%), alopecia (1%)
3. Endocrine & metabolic: Breast changes (discomfort: 5%), weight gain (4%), ovarian cyst (3%), decreased libido (2%)
4. Gastrointestinal: Nausea (4%), abdominal pain (2%)
5. Genitourinary: Irregular bleeding (1%)
6. Neuromuscular & skeletal: Weakness (2%)
7. Carbohydrate intolerance: May impair glucose tolerance

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Answer Key to Quiz in October Issue

1. A. F, B. T,C. T, D. F, E. T; **2.** O-ve Leucodepleted blood with Hct 75-80%; **3.** Birth at gestation between 20 0/7 to 25 6/7 weeks; **4.** A; **5.** A. Trisomy 18, B. Trisomy 21, C. Trisomy 18, D. NTD; **6.** In Step wise second trimester screening is offered only in low risk after first Tm screening and CVS is offered for high risk; **7.** C; **8.** Cut off is 32 weeks at diagnosis and 37 weeks at delivery; **9.** A. T, B. F, C. T, D. F; **10.** Computerized CTG; **11.** Fetal Alloimmune Thrombocytopenia; **12.** Lower Uterine Tract Obstruction **13.** Congenital Diaphragmatic Hernia; **14.** Strawberry Skull (Trisomy 18); **15.** Fetal reduction in triamniotic pregnancy

"Body, Mind and Soul"

The Mysterious Pineal Gland

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Pineal Gland is a tiny pea-sized gland shaped like a pinecone, residing in the center of brain, located at the back of the roof of the third ventricle. The Pineal Gland is vital for physical, mental and spiritual health, while also being a gateway to higher consciousness. Though the pineal gland couldn't be fully understood until the 20th century, descriptions of its anatomical location are included in the writings of Galen (ca. 130-ca. 210 CE), a Greek doctor and philosopher. Scientists considered it a mysterious organ. Unlike much of the rest of the brain, the pineal gland is not isolated from the body by the blood-brain barrier system. This also has a very rich blood supply. This is considered to be the connecting link between the physical and spiritual worlds. Considered the most powerful and highest source of ethereal energy available to humans, the pineal gland has always been important in initiating supernatural powers. Development of psychic talents has been closely associated with this organ of higher vision.

Traditionally, the pineal gland is said to be the third eye chakra, otherwise known as ***Ajna or the eyebrow chakra***, which is set back and between our two physical eyes. Scientific evidence supports the possibility that our ***third eye***, or pineal, was once our first eye. The pineal is made up of cells that have the same features as the rod-shaped light sensitive cells found in retinas. The pineal gland receives signals that travel down the optic nerves. It seems the primitive third eye functioned as a sight organ before our current set of eyes.

Physiological Functions

Pineal Gland synthesizes the hormone melatonin from the neurotransmitter serotonin. Melatonin production determines sleep-wake cycles and is purely determined by the detection of light and dark. The retina sends these signals to hypothalamus, which passes them on to the pineal gland. The more light brain detects, the less melatonin it produces, and vice versa. Melatonin levels are highest at night to help us sleep. Melatonin inhibits the release of gonadotropins, from the pituitary gland, affecting male and female reproductive organs. In this way, melatonin—and therefore the pineal gland—regulates sexual development. The pineal plays a major role in hibernation of animals, in metabolism and seasonal breeding.

The Spiritual Connect

While the physiological function of the pineal gland has been unknown until recent times, mystical traditions and esoteric schools have long known the significance of this. On a spiritual level, people in hundreds of cultures throughout the world have credited the pineal gland's proper functioning with spontaneous spiritual experiences. The pineal gland forms in a human embryo at 49 days during gestation – which just happens to also be the amount of time it takes, according to Tibetan Buddhists, for a soul to reincarnate into their next physical body. It has been written about in masked language, or painted in art throughout the ages, and represented in a staggering number of ways for thousands of years. The pineal gland is the only part of the brain that isn't bifurcated, and in Matthew 6:22 of the Christian bible it says, ***"The light of the body is the eye: if therefore your eye be single, your whole body shall be full of light."*** Egyptian, Druidic, Hindu, Hasidic, Islamic, Taoist, Mayan, Tibetan and Aboriginal cultures all acknowledge the pineal gland in their art and literature. Even the Catholic Pope's staff often has a pinecone on it. You can also see a pinecone in the Vatican flag.

According to theosophy, the pineal is an important psychophysiological centre or chakra and is the source of clairvoyance and intuition. It has also been described as ***"the principal seat of the soul,"*** and the portal to the higher dimensions, as the pineal, or third eye, provides perception beyond ordinary sight. Interestingly, the pineal gland has been linked to the production of the psychedelic DMT or dimethyltryptamine. It is believed that DMT is released during near death experiences, and this may explain the enhanced spiritual connection and awakening that takes place. The pineal and third eye, when awakened enable one to open up to have visions, clairvoyance and other psychic gifts.

Other functions of the pineal gland

The pineal gland has been linked to a range of other functions. These include:

Bone metabolism

Research on mice suggests that changes in the function of the pineal gland might affect bone metabolism. Oral melatonin supplements might help increase bone mass, which could be used in the future to protect against postmenopausal osteoporosis.

Mental health

Sleep and mental health are inextricably linked. Some mental health conditions have been linked to access to light. Seasonal affective disorder, for instance, is a form of depression that affects a person's mood and tends to occur when light levels are low. This may be due to changes in melatonin secretion. A 2017 review, however, found no evidence that melatonin had any effect on mood disorders

Pituitary gland function

Older research suggests that the pineal gland can alter the behavior of the pituitary gland.

Aging

As people age, the pineal gland tends to secrete less melatoninReduced levels of melatonin may help explain the aging process. Older adults tend to sleep less and may have trouble falling asleep. Changes in melatonin might explain this phenomenon

Sense of direction

Damage to this gland is associated with declines in the sense of direction. This suggests that the pineal gland may play a largely unrecognized role in spatial navigation.

Drug metabolism

Some drugs, including both recreational and prescription drugs, appear to alter the function of the pineal gland and change melatonin secretion patterns.

Pineal gland dysfunction

The pineal becomes steadily calcified with age. Through a poor diet, exposure to toxins in the environment and food we eat, stress and modern life, the pineal gland gets hardened, then calcified and eventually shuts down. It is also suppressed by electromagnetic fields (EMF) released by mobile phones and other wireless devices. The Pineal gland is especially sensitive to fluoride in the water. The Pineal Gland is very sensitive to chemicals and it is said that due to modern lifestyles, the pineal has shrunk. Indian Masters of the Vedic times were believed to have a pineal gland the size of a lemon. Today, our pineal gland is the size of small seed or pea.

The most prominent symptom of pineal gland dysfunction is a change in circadian rhythms. This might mean sleeping too much or too little, feeling active and restless in the middle of the night, or feeling sleepy at unusual times.

Other symptoms of a problem with the pineal gland include:

- Headache, nausea, vomiting, or tremor
- Difficulty with sense of direction
- Changes in fertility, menstrual cycle, or ovulation
- Osteoporosis
- Mental health issues, particularly seasonal symptoms

Considered to be a connection between physical and spiritual world, this scientifically poorly understood gland is important for physical, mental and spiritual well being. This gland can be protected by avoiding toxins in the food and surrounding atmosphere. This gland can be awakened through meditation, especially meditating with attention on the third eye area, which can be done in yoga practice and seated meditation.

Journal Scan

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1. Transl Pediatr. 2017 Oct;6(4):248-255.

Polycystic ovary syndrome in adolescence: Diagnostic and therapeutic strategies

Kamboj MK, Bonny AE

Controversy continues about the underlying etiopathogenesis, diagnostic criteria, and recommendations for polycystic ovary syndrome (PCOS) in adolescents. Recent literature has recognized these deficiencies and evidence based expert recommendations have become more available. The purpose of this chapter is to offer primary care providers a practical understanding and approach to the diagnosis and treatment of PCOS in adolescents. Although the presence of polycystic ovary morphology (PCOM) is included as a key diagnostic criterion of PCOS in adults, it is currently not recommended for the diagnosis in adolescents. As such, the diagnosis of PCOS in adolescents currently hinges on evidence of ovulatory dysfunction and androgen excess. Recommended evidence of ovulatory dysfunction includes: consecutive menstrual intervals >90 days even in the first year after menstrual onset; menstrual intervals persistently <21 or >45 days 2 or more years after menarche; and lack of menses by 15 years or 2-3 years after breast budding. Recommended evidence of androgen excess include: moderate to severe hirsutism; persistent acne unresponsive to topical therapy; and persistent elevation of serum total and/or free testosterone level. Importantly, a definitive diagnosis of PCOS is not needed to initiate treatment. Treatment may decrease risk of future comorbidity even in the absence of a definitive diagnosis. Deferring diagnosis, while providing symptom treatment and regular/ frequent follow-up of symptomology, is a recommended option. The treatment options for PCOS should be individualized to the presentation, needs, and preferences of each patient. Goals of treatment are to improve quality of life and long-term health outcomes. Lifestyle modifications remain first-line management of overweight and obese adolescents with PCOS. Combined oral contraceptives (COC) are first line pharmacotherapy for management of menstrual irregularity and acne, and metformin is superior to COCs for weight reduction and improved dysglycemia. COCs and metformin have similar effects on hirsutism, but often need to be paired with other treatment modalities to achieve further improvement of cutaneous symptoms. Clinicians should be cognizant that PCOS is associated with significant metabolic and psychological comorbidity and screen for these issues appropriately

2. J Endocrinol Invest. 2017 Nov 6. doi: 10.1007/s40618-017-0785-9.

The effect of vitamin D supplementation in combination with low-calorie diet on anthropometric indices and androgen hormones in women with polycystic ovary syndrome: a double-blind, randomized, placebo-controlled trial

Jafari-Sfidvajani S, Ahangari R, Hozoori M, Mozaffari-Khosravi H, Fallahzadeh H, Nadjarzadeh A

Purpose

Polycystic ovary syndrome (PCOS) is known as the most common endocrine disorder in reproductive age women. The aim of this studywas to evaluate the effects of vitamin D supplementation in combination with low-calorie diet on anthropometric indices, reproductive hormones and menstrual regularity in overweight and obese PCOS women.

Methods

In this randomized controlled clinical trial, 60 PCOS women with vitamin D insufficiency were randomly assigned to 12 weeks of either (1) weight-loss intervention + 50,000 IU/week oral vitamin D3 or (2) weight-loss intervention + placebo. At the beginning and end of the study, the anthropometric indices, body composition, 25-hydroxyvitamin D, total testosterone, dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG) and free androgen index (FAI) were measured and regularity of menses was compared among the two groups.

Result

After 12-week intervention, median of serum 25-hydroxyvitamin D3 significantly increased from 18.5 (10.75-20) ng/ml to 42.69 (34-53.25) ng/ml in vitamin D group compared to placebo group ($p < 001$). Moreover, there was a significant improvement in frequency regular menstrual cycle ($p = 0.01$). Mean of weight, body mass index, fat mass, waist and hip circumference and waist-to-hip ratio significantly decreased in both groups, but was not different between two groups. Mean

of total testosterone insignificantly decreased from 0.7 to 0.5 ng/ml in vitamin D group (p = 0.18). In addition, we did not observe significant differences regarding DHEAS, FAI and SHBG between two groups.

Conclusions

In women with PCOS, androgen profile did not change with vitamin D supplementation when combined with low-calorie diet, but menstrual frequency significantly improved

3. Fertil Steril. 2017 Jan;107(1):253-260.

Short-term therapy with combination dipeptidyl peptidase-4 inhibitor saxagliptin/metformin extended release (XR) is superior to saxagliptin or metformin XR monotherapy in prediabetic women with polycystic ovary syndrome: A single-blind, randomized, pilot study

Elkind-Hirsch KE, Paterson MS, Seidemann EL, Gutowski HC

Objective

To evaluate efficacy with the dipeptidyl peptidase-4 inhibitor saxagliptin (SAXA), metformin extended release (MET), and combination (SAXA-MET) in patients with polycystic ovary syndrome (PCOS) and impaired glucose regulation.

Design: Prospective, randomized, single-blind drug study.

Setting: Outpatient clinic.

Patient(S): Patients (n = 38) with PCOS (aged 18-42 years) and prediabetic hyperglycemia determined by a 75-gram oral glucose tolerance test.

Intervention(S): Patients were randomized to SAXA-MET (5 mg/2,000 mg), SAXA (5 mg), or MET (2,000 mg) for 16 weeks.

Main Outcome Measure(S):

Fasting and mean blood glucose, insulin sensitivity, insulin secretion, and insulin secretion-sensitivity index (IS-SI) by oral glucose tolerance tests. Free androgen index and lipid levels, average menstrual interval, and anthropometric measurements (body mass index, waist circumference, and waist/height ratio).

Result(S):

The study was completed by 34 patients. Nineteen patients had normal glucose tolerance: 3 of 12 (25%) on MET; 6 of 11 (55%) on SAXA; and 10 of 11 (91%) on SAXA-MET (SAXA-MET statistically superior to MET) at study completion. Body mass index, waist circumference, waist/height ratio, free androgen index, insulin sensitivity, IS-SI, and menses improved in all groups; however, IS-SI and menstrual regularity were significantly better with SAXA-MET vs. MET treatment. Triglyceride, triglyceride/high-density lipoprotein cholesterol ratio and mean blood glucose significantly declined in the SAXA-MET and SAXA groups only.

Conclusion(S):

This pilot work provides the first evidence regarding the effects of a dipeptidyl peptidase-4 inhibitor alone and in combination with MET in this patient population. Treatment with SAXA-MET was superior to either drug alone in terms of clinical and metabolic benefits in prediabetic patients with PCOS

4. Eur J Endocrinol. 2017 Nov;177(5):399-408.

Combined oral contraceptives plus spironolactone compared with metformin in women with polycystic ovary syndrome: A one-year randomized clinical trial

Alpañés M, Álvarez-Blasco F, Fernández-Durán E, Luque-Ramírez M, Escobar-Morreale HF

Objective

We aimed to compare a combined oral contraceptive (COC) plus the antiandrogen spironolactone with the insulin sensitizer metformin in women with polycystic ovary syndrome (PCOS).

Design

We conducted a randomized, parallel, open-label, clinical trial comparing COC (30 μg of ethinylestradiol and 150 μg of desogestrel) plus spironolactone (100 mg/day) with metformin (850 mg b.i.d.) for one year in women with PCOS (EudraCT2008-004531-38).

Methods

The composite primary outcome included efficacy (amelioration of hirsutism, androgen excess and menstrual dysfunction) and cardiometabolic safety (changes in the frequencies of disorders of glucose tolerance, dyslipidemia and hypertension). A complete anthropometric, biochemical, hormonal and metabolic evaluation was conducted every three months and data were submitted to intention-to-treat analyses.

Results

Twenty-four patients were assigned to COC plus

spironolactone and 22 patients to metformin. Compared with metformin, COC plus spironolactone caused larger decreases in hirsutism score (mean difference 4.6 points, 95% CI: 2.6-6.7), total testosterone (1.1 nmol/L, 0.4-1.7), free testosterone (25 pmol/L, 12-39), androstenedione (5.5 nmol/L, 1.8-9.2) and dehydroepiandrosterone sulfate (2.7 μmol/L, 1.4-4.0). **Menstrual dysfunction** was less frequent with COC plus spironolactone (OR: 0.06, 95% CI: 0.02-0.23). No differences were found in frequencies of abnormal glucose tolerance (OR: 1.7, 95% CI: 0.7-4.4), dyslipidemia (OR: 0.6, 95% CI: 0.2-1.8) or hypertension (OR: 0.3, 95% CI: 0.5-2.0). No major adverse events occurred and biochemical markers were similarly safe with both treatments.

Conclusions

COC plus spironolactone was more effective than metformin for symptoms of PCOS showing similar safety and overall neutral effects on cardiometabolic risk factors

AOGD Prize Winners 2017

Prize Name	Winners Name	Topics
Dr S N Mukherjee-Rotating Trophy	**UCMS & GTB Hospital**	Best AOGD Monthly Clinical Meeting
Research Paper-Best Competition Paper	**Gold** **Dr Nikita Bhartiya** (GTBH)	Effect of Yoga Therapy on 'Perceived Stress Score' in Low Risk Pregnancy: A randomized controlled trial
	Silver **Dr Megha Singhania** (GTBH)	Evaluation of Serum Biomarkers Leptin and Adiponectin as Risk Factors for Endometrial Cancer in Indian Women
	Bronze **Dr Divya Arora** (MAMC)	Complement C3 and C4 Levels in Women with Hepatitis E Virus Infection in Third Trimester of Pregnancy and its Association with Pregnancy Outcome
Dr Neera Agarwal's Medal-Best Paper on theme topic of Obstetrics (Maternal Health)	**Gold** **Dr Saloni Kamboj** (GTBH)	Association of Glutathione-S-Transferase Gene Polymorphism and Enzyme Activity with Organochlorine Pesticides in Pre-Eclampsia: A case-control study
Dr Neelam Bala Vaid's Medal-Best Paper on theme topic of Gynecology (Adolescent Health)	**Gold** **Dr Bhavana Girish** (AIIMS)	Post-Operative GNRH Agonist Therapy after Laparoscopic Cystectomy in Women with Stage III-IV Endometriosis: Does it improve fertility outcome?
	Silver **Dr Anurag Vashista** (SGRH)	Successful Management of Caesarean Scar Pregnancy by Medical and Surgical Methods- Case Series
Dr Suneeta Mittal's Medal-Population Stabilization	**Gold** **Dr Richa Sharma** (GTBH)	Incarcerated and Transmigrated Intrauterine contraceptive devices managed at a Tertiary care Hospital during 5 years- A Retrospective analysis
Dr U P Jha & Dewan Balakram's Medal (Best Presentation in Gynae Oncology)	**Gold** **Dr Rashmi Shriya** (GTBH)	Strength of Association of Colposcopic Findings by IFCPC and Swede Score with Cervical Histology
Dr U P Jha & Raj Soni's Medal (Best Oral/Video/Paper Presentation in Endoscopy)	**Gold** **Dr Shubhadeep Bhattacharjee** (Indira IVF Centre)	A randomised controlled trial to evaluate the relationship between size of ultrasonically detected hydrosalpinx mode of laparoscopic surgery(removal/ligation) and optimum time interval prior to embryo transfer in IVF-ICSI-ET cycles
Mr. S Bhattacharya & Dr Ganguly's Medal-Free Paper competition Miscellaneous Category	**Gold** **Dr K Aparna Sharma** (AIIMS)	Rh Isoimmunisation: The challenge continues
	Silver **Dr Kriti Tiwari** (MAMC)	Role of CB-NAAT in Detection of Genital Tuberculosis Amongst Women with Infertility: A prospective study
Poster Presentation	**Gold** **Dr Alpana Singh** (GTBH)	Study of Exposure to Second Hand Smoke in Pregnant Women and its Impact on Pulmonary Function and Pregnancy Outcome
	Gold **Dr Nidhi Gupta** (HIMSR)	Sexual Behaviour Among Adolescents: A Hospital Based Study
	Silver **Dr Arpita Dey** (HIMSR)	Analysis of Cesarean Deliveries in a Tertiary Care Centre using Modified Robsons Ten Group Classifi cation System
Poster Case Reports	**First Prize** **Dr Prashant Patil** (VMMC)	Uterus Didelphys with Obstructed Hemivagina and Ipsilateral Renal Agenesis (Ohvira Syndrome): A case report
	Second Prize **Dr Archana** (VMMC)	Merkel Cell Carcinoma of The Vagina – A case report
Dr Batra's Medal-Winning Team of AOGD Quiz	**Gold** **Dr Nikita Bhartiya** (GTBH) **Dr Saloni Kamboj** (GTBH)	Emergency Obstetrics

Proceedings of AOGD Monthly Clinical Meet

AOGD Monthly Clinical Meeting was held at Silver Jubilee Auditorium, ESI- Model Hospital, Basaidarapur on 1st November 2017

1. Borderline Ovarian Tumor in Unmarried Girl: A rare entity

Leena Wadhwa, Taru Gupta, Sonika Wahi, Sunita Jindal

Introduction: Borderline ovarian tumor constitute approximately 15 % of all epithelial ovarian cancers.80 % of them are discovered as stage 1. They occur predominantly in women < 40years. Most Common types are serous (53-65%)and mucinous(32-42%) and 10 year survival rate more than 95 %. Fertility-sparing surgery is done in young cases with early stage BOT.

Case Presentation: 23years unmarried girl presented to the Gynae OPD with C/O pain in right iliac fossa and weight loss since two months. She had regular menstrual cycles. No H/O tuberculosis.

General condition was fair, vitals were normal.No lymphadenopathy, thyroid and breast were normal.Chest &CVS- NAD. On per abdomen examination- A 15x10 cm abdomino-pelvic mass, cystic in consistency with restricted mobility non-tender with smooth surface and slightly irregular margins, was felt.On P/R- two separate masses one approx 10x8 cm felt in the left adnexal region, another mass 5x5 cm approx felt in the right adnexa restricted mobility, non-tender cystic in consistency felt. Uterus was normal size. Rectal mucosa free. On investigationTumour markers-CA 125-- 130 U/ml was raised.OnMRI Abdomen and Pelvis-Bilateral adnexa showed large encapsulated multiloculatedsolid, cystic masses closely abutting each other. Solid components were seen as papillary projections along the septae and walls of locules. Contents werehypointense on T2WI and isointense on T1WI. Scanty, compressed ovarian parenchyma was seen along periphery of both masses

Fertility sparing surgery that is bilateral ovarian cystectomy with preservation of normal ovarian tissue was done. Histopathology of Right side ovarian cyst revealed mucinous borderline tumor. Left side ovarian cyst report was benign mucinous cystadenoma. Omental biopsy showed noninvasiveimplants.

After 6 weeks of follow up CA125 was 50U/ml and after 12 weeksCA 125: 22 U/ml.Follow up Ultrasound & MRI Abdomen and Pelvis done at 12 weeks were normal.

Recurrence is high during first 2 post op years,so cases of BOT should be followed up till 2 years .Rate of recurrence of BOT is 7% after fertility sparing surgery group. Most common site of recurrence is remaining Ovary. Recurrence after BOT is mostly BOT only.Spontaneous pregnancy rate of 32-65% has been reported in BOT treated with fertility sparing surgery with a mean duration 15 months.

2. Pemphigoid Gestationis: A rare case

Swati Rai, Smita Gupta, Sangeeta Gupta

Introduction: Pemphigoid gestationisis a rare, autoimmune blistering dermatosis. It is unique in itself as it gets diagnosed primarily during pregnancy. It occurs in 1 in 50,000 pregnancies. The predominant symptom is pruritis. Patients generally present with a diffuse blistering eruption that start from periumbilical region and later on spread to involve whole of the body. The diagnosis is a clinical one and is confirmed by direct immunofluorescence demonstrating linear C3 pattern along dermo-epidermal junction. The mainstay of treatment is corticosteroid. Early diagnosis is essential as it helps us to treat early and hence reduce the maternal & foetal morbidity. An itch is a vague symptom but can be a clue to many diagnosis, therefore it should never be ignored in a pregnant female. The aim of this communication is to increase awareness among clinicians regarding this rare disorder.

Case Report: A 25 yr old normotensive G3P1L1A1 with one term vaginal delivery 3.5 yrs back and one 3month spontaneous abortion 1.5 yrs back presented in antenatal OPD at 33 wks of gestation with bullous pruritic lesions that started in the periumbilical region 15 days back and later on spread to involve the whole of the body. Patient didn't took any treatment except for some topical application from local doctor. She was referred to skin department and was misdiagnosed as a case of chicken pox and later on got admitted after 2 days as a case of pemphigoid gestationis in active stage and was started on systemic steroids. The dose of prednisolone was tapered and she was discharged on optimal maintenance dose. She was again admitted at 37 wks from antenatal OPD in view of intra hepatic cholestasis of pregnancy.

She was induced in view of IHCP and delivered a health male baby of 2.9 kg birth weight with no skin lesions. She developed flare up on postpartum day 2 and was again started on systemic steroids and was discharged on day 8.

To conclude a multidisciplinary approach is required for diagnosis , treatment and course of the disease from both dermatologist and gynaecologist view point.

3. Hemoperitoneum in Leiomyoma Uterus: A rare case report

Pratiksha Gupta, Sanjana Wadhwa

Leiomyoma are most common benign tumour of female genital tract. Mostly these present with menstrual irregularities, pain and pressure symptoms. Leiomyoma can

present atypically with haemorrhage and hemoperitoneum. We are reporting one such case in perimenopausal women.

Case Report: A 43year old lady presented with chief complaints of severe pain in abdomen and vomiting since 4days. Patient was clinically pale and vitally stable. On P/A, midline tender firm mass of 24weeks size was palpable with restricted mobility. On P/V, uterus was not felt separate from mass which enlarged to 24weeks uterine size and fullness was present all through the fornices. Hemoglobin was 4gm%. It was diagnosed on ultrasound and MRI as large subserous fibroid of 15x14cm arising from fundus of uterus with gross fluid in peritoneum. Laprotomy confirmed findings and total hysterectomy was done along with evacuation of 2500cc hemoperitomeum.

This is an interesting, rare but possible fatal complication of large leiomyoma. Only 100 cases have been reported in literature so far. In large leiomyoma there is increased diameter of arteries and increased vascularity. Spontaneous bleeding is likely to occur from torn enlarged veins coursing over surface of subserous leiomyoma resulting in acute abdomen, hemoperitoneum and hypovolemic shock. It is rare atypical fatal complication and should be kept as differential diagnosis and treated as emergency like in our case, patient underwent emergency laparotomy.

AOGD Monthly Clinical Meeting was held at Maulana Azad Medical College and LNJP Hospital on 24th November 2017

1. Atypical Case of Mullerian Agenesis with Peritonitis

Anjali Tempe, Devender Kumar, Nilanchali Singh, Aparna Setia, Komal Rastogi

Introduction*:* Cervical agenesis is defined as a congenital malformation of the female genital tract leading to an absent cervix due to failure of canalization of the paramesonephric ducts during fetal development. Its incidence is estimated to be 1 in 80,000 females. In 52% cases cervical agenesis is associated with vaginal deformities such as hypoplasia.

Case Report*:* We are presenting a case of 18 years old, unmarried female belonging to rural background who presented with chief complaints of cyclical pain abdomen since three years, continuous pain abdomen, associated with nausea & vomiting on and off and generalized weakness since one month. She was investigated one month back in private hospital. She has sought no treatment earlier. She was diagnosed as a case of Mullerian anomaly with absent right kidney with hemorrhagic cyst on USG & MRI at the private hospital. She was admitted for one week in view of pain and vomiting at private hospital, before presenting to us. She was managed conservatively and referral to us.

At presentation, she has tachycardia, fever and dehydration. She was pale and cachexic. Mild tenderness in lower abdomen; Gaurding & rigidity in umbilical & Left lumbar region; vague fullness s/o mass at level of umbilicus on left side. There was small i.e. 2 cm vaginal opening. Her investigations revealed anaemia and raised leucocyte count, dyselectrolytemia. Fever investigations were negative. USG & MRI revealed absent right kidney with a bulky uterus with hypoechoic fluid collection within suggestive of hematometra, with a dilated tubular structure in left adnexa suggestive of hematosalpinx. Diagnosis was hematometra (?Hemi-uterus) with left hematosalpinx with cervical and vaginal atresia/ agenesis with right renal agenesis with presentation as peritonitis. Supportive therapy was given. Though she was planned for conservative surgery with vaginal reconstruction, it could not be performed due to peritonitis, poor general condition of the patient and long atretic area between hematometra and small lower third vagina (4 inches). A hemi-hysterectomy with left tubo-ovarian mass removal was performed for her. Patient was discharged later in a satisfactory condition with plan for vaginoplasty later.

Determinants of successful management in such cases are correct pre-operative assessment & recognition of assoc. anomalies, intra-operative recognition of all anomalies, optimal surgery to restore reproductive, sexual, and over-all health (vary from conservative treatment to radical surgeries), post-operative treatment, support, counseling & follow-up. The aim of our management should be to give the female a healthy sexual life and successful reproductive outcome with good psychological support.

2. Androgen Insensitivity Syndrome with Seminoma – A case report

Deepali Mittal, Preeti Singh, Asmita Rathore

Introduction: Androgen insensitivity syndrome is a rare X-linked recessive disorder of sex development caused due to androgen receptor dysfunction. As the testes remain undescended, the risk of malignancy increases with age. The risk of malignancy till 25 years is estimated to be 3.6%, which increased to 33% at age of 50 years.

Case Summary: A 33 years old patient raised as a female presented to OPD with complaint of abdominal mass.At age of 19 years she was a mis-diagnosed as case of primary amenorrhoea with mullerian agenesis. On physical examination she had well developed breast with absent axillary and pubic hairs. She had adequate length vagina with absent cervix. On clinical suspicion of androgen insensitivity syndrome karyotyping was done which was reported as 46,XY. On further work up all laboratory and radiology findings were conclusive of androgen insensitivity syndrome with development of malignant tumor in undescended testis. The tumor was excised along with gonadectomy of normal looking gonad in right

inguinal fossa. The histopathological evaluation of tumor and right gonad was reported as seminoma and testis with absent spermatogenesis respectively. Patient was started on chemotherapy with Bleomycin, Etoposide and Cisplatin regimen along with estrogen replacement therapy.

Conclusion: In every patient presenting with complaint of primary amenorrhoea, possibility of androgen insensitivity syndrome should be kept in the mind. As in our patient in her initial work up at age of 19 years if she had been diagnosed with androgen insensitivity syndrome, early gonadectomy would have prevented development of seminoma. Thus we conclude, once this syndrome is diagnosed the gender identity should be maintained and early gonadectomy followed by supplemental estrogen replacement therapy is recommended as one attain puberty because risk of malignancy increases with advancement of age.

3. Experience of Hepatitis E in Pregnancy

Ashok Kumar

Hepatitis E virus (HEV) infection is one of the major public health diseases in many developing countries with water-borne epidemics. Although largely a self-limited infection, it results in morbidity and mortality, especially among pregnant women.

In our experience of Hepatitis E infection during Pregnancy, 916 pregnant women with jaundice were observed and data analyzed. Mean age and mean gestational age were 24.67±3.63 years and 35 weeks and 3 days. Of these, IgM HEV positivity was 66.67% (610/916). On analyzing the clinical presentation, Acute Viral Hepatitis (AVH) was observed in 80.82% (493/610) and Fulminant Hepatic Failure (FHF) in 19.18% (117/610). Total number of AVH and FHF cases having HEV RNA positivity were 68.36% (337/493) and 60.68% (71/117) respectively. The maternal and fetal mortality was 31% and 37% cases of HEV infection. All cases belong to HEV genotype 1a.

Various hypotheses have been put forward by our studies to explain the pathogenesis of fulminant and fatal hepatitis E in pregnancy. Overall prevalence of seropositive HEV IgG was 33.67% among the pregnant women. Higher HEV viral load was found in pregnant patients than in non-pregnant patients. Pregnancy appeared to be one of the risk factors for delayed elimination of the virus.

The severe liver injury because of HEV infection during pregnancy may be related to one of several possible host factors, such as differences in immune and hormonal factors occurring during pregnancy. HEV-infected pregnant women have diminished cellular immunity as evidenced by decrease in CD4, increase in CD8 cell count and lowered CD4/CD8 cell ratio along with high levels of steroid hormones during pregnancy. All these events might influence viral replication/expression during pregnancy. Reduced expression of Progesterone receptors and Progesterone induced blocking factors, higher IL-12/IL-10 ratio and high viral load results in poor pregnancy outcome in Hepatitis E. Significantly higher levels of IFN-g, TNF-a, IL-6 and TGF-b1 were found in pregnant women with HEV infection compared with that of non-pregnant women and AVH and FHF groups of HEV infected pregnant women compared to that of non-pregnant women and controls. Cytokines are associated with increased severity of disease in terms of occurrence of FHF and adverse pregnant outcomes in pregnancies complicated with HEV infection. Higher frequency of high cytokines producing genotypes were observed in pregnant women with HEV infection compared to non-pregnant women with HEV infection, pregnant women not infected with HEV and controls and were found to be associated with adverse pregnancy outcome (preterm delivery, low birth weight newborns, small for date, and fetal loss). A complex interaction of viral factors and cytokine levels culminating into an altered immune response during pregnancy may be responsible for the severe liver injury seen in HEV infection during pregnancy resulting in high maternal mortality and adverse pregnancy outcome. Malnutrition might confer a higher predisposition for HEV infection during pregnancy. Lower levels of nutritional parameters are associated with increased severity in terms of occurrence of ALF and predispose towards it during HEV infection.

It is possible that low nutritional status involves in mechanism that altered immune response during pregnancy which may be responsible for the severe liver injury seen in HEV infection during pregnancy.

Oxidative stress is present in HEV infection during pregnancy, as shown by low levels of reduced glutathione (GSH) and is associated with adverse pregnancy outcomes. Serum GSH ≤10.88 ng/mL during pregnancy can be used for risk stratification for HEV infection. Pregnant patients with hepatitis E are treated with only supportive management, which often does not cure the disease. Maintaining antioxidant defense system in HEV-infected pregnant patients by supplementation with antioxidant vitamins may be worthwhile.

The relationship between hepatitis E and pregnancy is quite interesting. Sporadic hepatitis E infection is associated with increased incidence and severity in pregnant women. High vertical transmission rate indicates the importance of vertical transmission of HEV infection. Common complications during pregnancy may include death of the mother and fetus, abortion, premature delivery, or death of a live-born baby soon after birth. HEV infection is a significant health issue and a major area of concern particularly in pregnancy. Maintaining hygienic practices and access to potable water are some of the important preventive measures to decrease the maternal & perinatal mortality and morbidity of HEV infection.

Quiz Time: *Tick it, Fill it, Click it, Whatsapp/ Email it*

Rashmi, Bindiya Gupta

Assistant Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences & Guru Teg Bahadur Hospital, Delhi

1. Fill in the blanks
   a) Kupperman's score is _____
   b) Any 4 components of vaginal health index
   c) STRAW stands for
   d) APRELA in menopausal hormone therapy contains _____
   e) Two multiphasic oral contraceptive pills

2. What is false about Ormeloxifene
   a) Ormeloxifene is recently added in the National Family Planning Programme as 'CHHAYA' as an oral contraceptive.
   b) Its contraceptive dose is 30 mg taken twice weekly or the first three months and then weekly thereafter.
   c) Ormeloxifene causes anovulation
   d) Ormeloxifene should be avoided in cervical hyperplasia, jaundice or liver disease

3. Surgical management of pituitary microadenoma is indicated in all except
   a) Persistent visual field defect
   b) DA resistance/intolerance
   c) Unstable with neurological symptoms
   d) Long standing hypogonadism

4. Write true of false
   a) Polycystic ovary morphology (PCOM) is included as a key diagnostic criterion of PCOS in adolescents
   b) Metformin is not superior to COCs for weight reduction and improved dysglycemia in PCOS
   c) The terminal half-life of dienogest is 10 hours
   d) Dienogest has antiproliferative, immunologic, and antiangiogenic effects.

5. Name 4 conditions which are poor responders to ovulation induction

   _____

6. Failure to ovulate is termed as _____ while failure to conceive despite ovulation with CC is termed as _____

   _____

7. Name two second generation SERMs _____.

   _____

8. SERM's used in vulvovaginal atrophy are _____ and _____

   _____

9. Full form of TSEC:

   _____

10. Ennumerate three clinical applications of SPRM:

    _____

11. What is false about insulin sensitizers and ovulation induction:
    a) Metformin alone may be beneficial over placebo for live birth, although the evidence quality was low.
    b) Clomiphene citrate is not preferable to metformin for ovulation induction in obese women with PCOS
    c) Metformin plus FSH was associated with a higher cumulative live birth rate when compared with only FSH in PCOS women
    d) Adding Metformin to clomiphene does not improve overall live births compared with clomiphene alone.

Tick the MCQs and fill in the blanks.
Click a pic and whatsapp or email to us
Whatsapp Nos.: 9810645212, 9810719002
Email: info@aogd.org

Refer page 42 for Previous answer key.

Royal College of Obstetricians & Gynaecologists AICC Northern Zone India

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SOCIETY OF FETAL MEDICINE (SFM)

Membership Benefits:

- Being part of a fraternity of likeminded individuals
- Free access to quarterly meetings
- 20% discount on all SFM CMEs
- 20% discount at the International Congresses of the Society of Fetal Medicine
- Regular emails on Fetal Medicine activities all over the world
- Free access to the website
- Substantial discount on the subscription to the Journal of Fetal Medicine.

For membership, kindly contact Vishal Mittal at +919312227181 or send an email at sfmsecretariat2017@gmail.com. Online membership can be taken through our website www.societyoffetalmedicine.org

Membership Charges:

Membership for 10 years: INR 4000/-; One Time Processing Fee: INR 500/-; Total: INR 4500/-

Please make Cheque/ Draft in favour of *"Society of Fetal Medicine"* payable at *"New Delhi"& send to the "Secretariat, C584, Defence Colony, New Delhi-110024, India."*

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