



AOGD BULLETIN

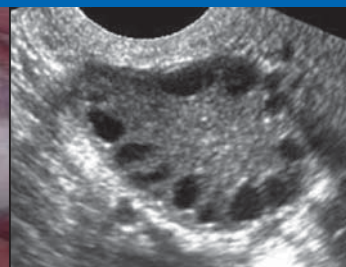
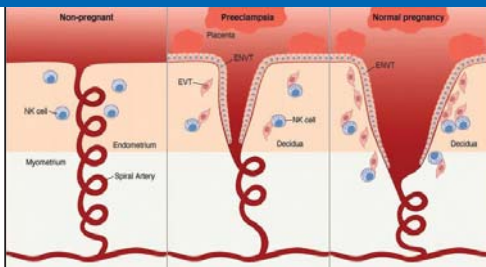
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AOGD Theme 2018-19
Empowering Providers:
Enhancing Women's Health

Issue: Current Update
Preclampsia
Polycystic Ovarian Disease



AOGD SECRETARIAT

Department of Obstetrics and Gynecology
Lady Hardinge Medical College & Smt. Sucheta Kriplani Hospital, New Delhi-110001
secretarylhaogd2018@gmail.com

www.aogd.org

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Department of Obstetrics and Gynecology

Lady Hardinge Medical College & Smt. Sucheta Kriplani Hospital, New Delhi 110001

Tel No: 011-23408297; Email: secretary@haogd2018@gmail.com

www.aogd.org

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AOGD BULLETIN

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Editor

Dr Ratna Biswas

Ph. No. 011-23408297; Email: secretary@haogd2018@gmail.com

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President's Message



Dear AOGD Members,

Greetings!

It is my proud privilege to represent this esteemed Association of Obstetricians & Gynaecologists of Delhi as President for the year 2018-2019, and I am thankful for the opportunity and confidence bestowed upon me to serve AOGD along with my team members from Lady Hardinge Medical College.

This year's theme " 'Empowering providers, Enhancing women's health' " is aimed to take care of all stakeholders involved in looking after women's health. The aim is to enrich the providers with opportunities to enhance their skills, learn what's new from across the globe and be updated with evidence based practices.

We have planned to organise CME, workshops and public awareness programmes to achieve our aim. An academic bonanza is being planned for the annual conference in last week of November 2018 at India Habitat Centre and hope to see you in large numbers. This time again we hope to come up to your expectations.

The editorial team is working hard to give you the current updates in topics of clinical interest with information and keeping you updated with events. Hope it will be an enjoyable and informative reading.

All of us have to work together to meet our targets for enhancing women's health and nothing can be achieved alone. I appeal to all AOGD members to come forward and participate with full strength in all endeavours. I also request you to give your inputs because it is the team effort which will allow us to scale heights in women's health.

With blessings and guidance from my seniors, patrons, advisors and executive council members with their vast experience I hope we will be able to provide an informative, fruitful, and enjoyable journey of AOGD for the year 2018-2019.

Regards,

Dr Abha Singh
President AOGD

Vice President's Message



Dear AOGD Members

Greetings

Welcome aboard on the yearlong academic journey with Team LHMC. Year after year AOGD has strived to keep its members updated with the latest. It syncs its activities with programmes and agendas of the Government and FOGSI from time to time with the common goal of enhancing Women's Health. This year team LHMC proposes to empower the providers with not only knowledge and clinical skills but also with soft skills such as communication skills, healthy interpersonal interactions, ways of de-stressing, anger management etc. These are neither a part of curriculum nor formally taught during training to health care providers. Regular enrichment of skills is essential for not only providing quality care to the patient which is currently a top agenda of Government, but also to avert problems like violence against health care providers and medicolegal cases. This is vital in the present times when the medical profession is sailing through turbulent waters and adversely affecting the mental and physical health of doctors and eroding the doctor patient relationship.

This month is being celebrated as Preeclampsia awareness month I congratulate the editorial team for bringing out their first issue of AOGD bulletin on Preeclampsia and PCOS under the guidance of Dr Ratna Biswas. The previous editorial team under Dr Bindiya and Dr Rashmi did a commendable job and I am sure that the present team will match the high levels set by them. Team LHMC looks forwards to a significant and satisfying term.

Dr Manju Puri
Vice President AOGD

Secretary's Message



Dear AOGD members,

Warm greetings from the AOGD secretariat at Lady Hardinge.

It is indeed an honour and proud privilege to address AOGD through these lines as its honorary secretary. With dedication and diligence we hope to meet the high standards set in front of us by our predecessors.

'Empowering providers, Enhancing women's health' is our motto for the year.

Empowering all the providers and provide them guidance, be it to enhance their basic core skills, hone up their operative skills, and keep them updated on recent trends is the target for this year through CMEs, workshops and symposiums.

Public awareness and community outreach is also a very important part of preventive health care. We plan to address this through various subcommittees of AOGD and their programmes.

Mental well being of the providers is also important, therefore we started the year with a talk on 'Healing the Healers' by Dr Mohit Gupta on 12th April at Lady Hardinge addressing how to deal with day to day stresses and improving patient doctor relationship. This was followed by FOGSI FORCE Rajdhani a FOGSI Medical Education Committee initiative for post graduate teaching.

The editorial team under the able guidance of Dr Ratna Biswas has brought up a current update on PCOS and Preeclampsia in this issue and hope it becomes a ready reckoner and keeps you updated.

An academic feast awaits you all at the Annual Conference planned in November at India Habitat center. Hoping to see you all in large numbers as it will be a pleasure to interact with all of you.

We will be in touch with you through AOGD website, SMS, emails, and through the bulletin. Kindly inform about your changed address or contact details. The information may be sent to the mail id secretarylhaogd2018@gmail.com

You can also discuss your difficult cases and situations and put it on the website or mail us at the email id given above; we will have experts answering you back as soon as possible.

I am thankful for the inputs and guidance from our President Dr Abha Singh, Vice president Dr Manju Puri, and Scientific advisor Dr Reena Yadav and also to team Hardinge for all hard work and cooperation.

Hoping for an enjoyable learning year ahead

Dr Kiran Aggarwal
Secretary AOGD

Monthly Clinical Meeting

Monthly Clinical Meet will be held at BLK Super Speciality Hospital, New Delhi
on Friday, 25th May, 2018 from 04:00pm to 05:00pm.

Editorial Team's Message



Dr Ratna Biswas
Editor



Dr Pikee Saxena



Dr Sharda Patra
Co-Editors



Dr Swati Agrawal

Dear Readers,

Greetings from the Editorial team!

It gives us great pleasure to bring forth the first issue of AOGD bulletin for this innng of AOGD office at Lady Hardinge Medical College & Smt. SSK Hospital. We shall be focussing on one area from Obstetrics and one from Gynaecology in each issue and discuss the subject in depth under the subheadings of standards of care, recent advances, controversies and case approach. Our focus for this issue is on Preeclampsia and PCOS.

Preeclampsia affects 8-10% of pregnancies worldwide and is the cause of considerable maternal as well as fetal morbidity and mortality. In order to raise awareness about preeclampsia and its global impact on maternal and child health, many international organizations such as the Population Council and USAID have declared 22nd May as the World Preeclampsia Day. Keeping this in mind we are celebrating this month as the Preeclampsia Awareness Month. The articles in this issue comprise of Best clinical practice guidelines for managing preeclampsia; Recent AHA guidelines & results of the CHIPS trial; Controversies on clinical utility of practice models for severity of preeclampsia and Case approach to a patient of preeclampsia with neurological symptoms.

Polycystic ovarian syndrome affects 12-18% of women in the reproductive age group and these patients constitute a major chunk of the population attending the gynaecological OPDs. This issue includes Best clinical practice for the management of adolescent PCOS; Recent advances in the management of infertile PCOS; Controversies in the diagnosis of insulin resistance in PCOS and Case approach to a patient with hyperandrogenism.

We have introduced a section "From distress to de-stress" which will contain a series of motivational lectures by Dr. Mohit Gupta. It will help you to connect with your inner self and take you to a voyage of self discovery.

The maze of knowledge-crossword and the pictorial quiz is bound to rack your brains and keep you engaged.

I hope this bulletin meets your expectations. We look forward to comments and suggestions from you to help us in providing you a memorable reading experience.

Happy Reading!!

Editorial Team

Standards of Care in Pre-eclampsia and Eclampsia



Dr Reena Yadav

Reena Yadav

Director Professor, Department of Obstetrics and Gynaecology, Lady Hardinge Medical College & SSK Hospital, New Delhi

Hypertensive disorders of pregnancy affect 10% of all pregnant women all over the world. Pre-eclampsia is a serious condition that starts after 20th week of pregnancy. High blood pressure is the main contributing factor. The rate of Pre-eclampsia has increased in the last two decades and is leading cause of maternal and perinatal morbidity and mortality¹. The majority of which are avoidable through the provision of timely and effective care to the women presenting with these complications.

Diagnostic criteria for pre-eclampsia: Preeclampsia is a pregnancy specific hypertensive disorder with multisystem involvement. It usually occurs after 20 weeks of gestation and can be superimposed on another hypertensive disorder. Preeclampsia is defined by occurrence of new onset hypertension plus new onset proteinuria. These two criteria are considered classic definition of preeclampsia. Some women present with hypertension and multisystem signs usually indicative of disease severity in the absence of proteinuria. It may be thrombocytopenia, impaired liver function, new development of renal insufficiency, pulmonary edema or new onset cerebral or visual disturbance¹. (Table 1)

Table 1: (ACOG Guidelines) for diagnosis of preeclampsia

Blood pressure	<ul style="list-style-type: none"> • ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic on two occasions at least 4 hrs apart after 20 weeks of gestation in a woman with previously normal BP • ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic, hypertension can be confirmed with in short interval to facilitate timely antihypertensive therapy
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And

Proteinuria	<ul style="list-style-type: none"> • ≥ 300 mg per 24 hrs urine collection or • Protein /Creatinine ratio ≥ 0.3 • Dipstick reading of 1+ used only if other methods N/A
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Or in the absence of proteinuria, new onset hypertension with new onset any of the following:

Thrombocytopenia	Platelet count $< 100,000$ /microliter
Renal insufficiency	Serum Creatinine > 1.1 mg/dl or a doubling of serum Creatinine concentration in the absence of other renal disease
Impaired liver function	Elevated liver transaminases to twice normal concentration
Pulmonary edema	
Cerebral and visual symptoms	

Guideline development group of NICE classify hypertension in to mild if Systolic/diastolic BP is between 140-149/90-99 mmHg, Moderate if between 150-159/100-109 mmHg and severe if BP is $\geq 160/110$ mmHg².

Traditionally preeclampsia is classified mild in the absence of severe manifestation; ACOG recommends that instead the term preeclampsia without severe feature be used. From recent studies it has been found that there is minimal relationship between the quantity of urinary protein and pregnancy outcome in preeclampsia, massive proteinuria has been eliminated from the consideration of preeclampsia as severe. Also, because FGR is managed similarly in pregnant woman with or without preeclampsia, it has been removed as a finding indicating severe preeclampsia

Eclampsia is convulsive phase of the disorder and is the more severe manifestation of the disease. It is often preceded by premonitory events such as severe headache and hyperreflexia, but it can occur in the absence of warning signs and symptoms.

Prediction of Preeclampsia: Utility of uterine Doppler studies to predict preeclampsia has been extensively studied. Uterine artery studies are better at predicting early onset preeclampsia than term preeclampsia. Alteration in the number of circulating antiangiogenic proteins sFlt-1 and soluble endoglin and proangiogenic proteins PIGF and VEGF have been evaluated as potential biomarker for use in preeclampsia. Alteration in the concentration precede the clinical onset of preeclampsia by several weeks to months, their prediction potential has been evaluated in many studies. However sFlt-1 is altered 4-5 weeks before the onset of clinical symptoms, it is not useful when used alone as screening test earlier in gestation. In contrast PIGF concentration begin to decrease 9-11 weeks before the appearance of hypertension and proteinuria. A number of studies evaluated first trimester use of PIGF that reveal at most modest predictive values for early onset preeclampsia. Combining uterine pulsatility index, mean arterial BP, PAPP-A, serum free PIGF, BMI and presence of Nulliparity or previous preeclampsia the detection rate of early preeclampsia was 93.1%³. Although the results of these studies are promising they are not recommended for clinical practice because evidence that maternal -fetal outcome are improved by early screening is still lacking. "First Trimester Risk Assessment for Early-Onset Preeclampsia, "issued

by ACOG and endorsed by the Society for Maternal-Fetal Medicine states that taking a detailed medical history is the best and only recommended screening for preeclampsia risk in the first trimester. It should remain the method of screening for preeclampsia. With ACOG recently recommending an expanded list of risk factors for preeclampsia including history of preeclampsia, multifetal gestation, chronic hypertension, diabetes, renal disease, and autoimmune disease. It does not recommend screening to predict preeclampsia beyond obtaining an appropriate medical history to evaluate for risk factors. Quality of evidence - Moderate. Strength of recommendation - Strong

Prevention of Preeclampsia: Strategies to prevent preeclampsia has been studied extensively. No intervention to date has been proved unequivocally effective. One of the hypothesis in the pathogenesis of preeclampsia is the alteration of prostacyclin - thromboxane balance. Low dose aspirin, an anti-inflammatory agent that blocks production of thromboxane has been studied for prevention of preeclampsia. Cochrane metaanalysis of these studies found a 17% reduction in the risk of preeclampsia with the use of aspirin with a significant risk reduction in women who are at high risk of the disease⁴. In a multicenter RCT trial by Daniel L R et al, it was concluded that administering low dose aspirin 150mg starting between 11 to 14 weeks and continued till 36th week led to 62% reduction on rate of preterm preeclampsia⁵. Given the modest but significant protective effect, low dose aspirin prophylaxis may be considered as primary prevention of preeclampsia in women with high baseline risk (medical history of early onset preeclampsia and preterm delivery before 34 weeks of gestation or preeclampsia in more than one prior pregnancy), should be initiated in the late first trimester. Quality of evidence-Moderate. Strength of recommendation -Qualified

Several studies have examined the effectiveness of calcium supplementation to prevent preeclampsia. Its supplementation is expected to be of benefit in women who have a nutritional deficiency of calcium. Thus calcium supplementation (1.5 -2gm) may be considered in pregnant women from populations with low baseline calcium intake⁶. Supplementation with Vitamin C and Vitamin E did not reduce the risk of preeclampsia or improve maternal and fetal outcomes in the review of randomized controlled trials⁷. Administration of these vitamins is not recommended for prevention of preeclampsia -Quality of evidence -high. Strength of recommendation -strong

Use of diuretics and restriction of dietary salt is not recommended for prevention of preeclampsia, Quality of evidence - Low. Strength of recommendation - Qualified

Although bed rest has been suggested as preventive strategy, the evidence for this is scarce. However,

regular exercise has been hypothesized to prevent preeclampsia by improving vascular function. Thirty minutes of moderate exercise on most days is currently recommended during normal pregnancy. It is hypothesized to stimulate placental angiogenesis and improve maternal endothelial dysfunction. Small clinical trials have evaluated the utility if moderate exercise in prevention of preeclampsia but no reliable conclusion about its efficacy is made⁸

Management of Preeclampsia without Severe Features

At the time of diagnosis all women should have a complete blood count with platelet count and assessment of serum creatinine and liver enzymes levels, urine proteins 24 hours collection or protein / creatinine ratio. And women be asked about symptoms of severe preeclampsia. Fetal evaluation should include ultrasonographic evaluation of estimated fetal weight and amniotic fluid index, Nonstress test and Biophysical Profile if NST is nonreactive. Best practice indicates hospitalization and delivery for one or more of the following²;

- 37 weeks or more of gestation
- Suspected abruption placentae
- 34 weeks or more plus any of the following
- Progressive labour or rupture of membrane
- USG estimate of fetal weight less than 5th percentile
- Oligohydroamnios (AFI<5)
- Persistent BPP 6/10

Continued Evaluation in women with preeclampsia without severe features can occur at hospital or at home with restricted activity and serial maternal and fetal evaluation

Fetal evaluation includes daily kick count, ultrasonography to determine fetal growth every 3 weeks and AFI once a week and NST twice weekly. Frequency of these tests may be modified based on subsequent clinical findings.

Daily maternal blood pressure monitoring and evaluation of laboratory parameters is suggested at least once a week. Frequency of these may be modified based on subsequent clinical findings. Women are instructed to report symptoms of severe preeclampsia (severe headache, visual symptoms, epigastric pain, shortness of breath). The development of new sign or symptoms of severe preeclampsia or severe hypertension or evidence of fetal growth restriction require immediate hospitalization. In additions increased concentration of liver enzymes or thrombocytopenia require hospitalization.

Antihypertensive Therapy

Antihypertensive therapy is used to prevent severe

gestational hypertension and maternal hemorrhagic stroke. Overall there is no consensus regarding the management of non severe hypertension. Therapy may decrease progression to severe hypertension but may also be associated with impairment of fetal growth. A Systemic review concluded that it is unclear whether antihypertensive therapy is worthwhile. These reviews concluded that there is insufficient evidence that treatment of non severe hypertension improves maternal and neonatal outcomes⁹. The national institute for health and clinical excellence guidelines recommended treatment of BP levels at 150mmHg systolic or 100mmHg diastolic or both². The objective of treating severe hypertension are to prevent potential cardiovascular (heart failure, pulmonary edema), renal (renal failure) or cerebrovascular (Ischemic or hemorrhagic) complications related to uncontrolled severe hypertension. These life threatening maternal complications justify recommendation of the use of medication to lower blood pressure to safe range even though the magnitude of this risk is unknown.

As far as bed rest is concerned there is insufficient evidence to provide guidance for clinical practice, suggesting that bed rest should not be routinely recommended for management of hypertension in pregnancy. Prolonged bed rest for duration of pregnancy increases the risk of thromboembolism.

Fetal testing—Limited to no data exist regarding when to start fetal testing, the frequency of testing and which test to use in the absence of fetal growth restriction. ACOG recommends use of USG to assess fetal growth and antenatal testing to assess fetal status in preeclampsia without severe features. If evidence of fetal growth restriction is found in women with preeclampsia, fetoplacental assessment that includes umbilical artery Doppler velocimetry as an adjunct antenatal test is recommended

Intrapartum Management

Timing of Delivery: In women with Preeclampsia without severe features and gestation less than 37 weeks, expectant management with maternal and fetal monitoring is suggested. Risk include development of severe hypertension, eclampsia, HELLP syndrome, abruptio - placentae, FGR and fetal death. Immediate delivery is associated with increased rate of NICU admission, neonatal respiratory complications. Considering risk -benefit ratio between two management plans ,available data suggest that balance should be in favour of continued monitoring and delivery at 37weeks of gestation in the absence of abnormal fetal testing or other severe conditions. Quality of evidence - Low, Strength of recommendation - Qualified

Use of Magnesium Sulfate

Although universal use of magnesium sulfate therapy

in preeclampsia without severe feature is not recommended. However clinical course of this condition can suddenly change during labour, women must be monitored closely for early detection of progression to severe disease. Monitoring of maternal BP and symptoms during labour and delivery as well as in immediate postpartum period is recommended. Magsulf therapy should be initiated if there is progression to severe disease. Quality of evidence - Low. Strength of recommendation - Qualified

Severe Preeclampsia

Severe preeclampsia can result in both acute and long term complications for both the women and her new born. Maternal complications include pulmonary edema, myocardial infarction, ARDS, coagulopathy, severe renal failure and retinal injury. These complications are more likely to occur in the presence of preexisting medical disorder and with acute maternal organ dysfunction related to preeclampsia. Fetal and neonatal complications of severe preeclampsia result from exposure to uteroplacental insufficiency or from preterm birth or both. Delivery is recommended when gestation is 34weeks or more in severe preeclampsia and immediately with any of these complication irrespective of period of gestation.

Table 2: Management of severe preeclampsia at less than 34weeks of gestation¹

<ul style="list-style-type: none"> • Observe for first 24-48hours • Corticosteroids, Magnesium sulfate prophylaxis and antihypertensive medications • Ultrasonography, monitoring of FHR, Symptoms and laboratory tests 		
Contraindication to continued expectant management- Deliver once maternal condition is stable		Expectant management
<ul style="list-style-type: none"> • Eclampsia • Pulmonary edema • DIC • Uncontrolled severe hypertension • Persistent symptoms • HELLP or Partial HELLP • Significantly deteriorating renal function • PROM 	<ul style="list-style-type: none"> • Nonviable fetus (<24weeks) • Severe Oligohydroamnios • Abnormal fetal test results • Abruptio placentae • Intrapartum fetal demise 	<ul style="list-style-type: none"> • Facilities with adequate maternal and neonatal intensive care resources • Fetal viability<34weeks • Inpatient only and stop magnesium sulfate • Daily maternal - fetal tests • Vital signs, symptoms and blood tests • Oral Antihypertensive drugs

Deliver if

- Achievement of 34weeks
- New onset contraindications to expectant management
- Abnormal maternal -fetal test results
- Labour or premature rupture of membrane
- Delivery decision should not be based on the amount of proteinuria or change in the amount of proteinuria (Quality of evidence-Moderate, Strength of recommendation - Strong)

Maternal Assessment

- Vital signs, fluid intake and urine output should be monitored at least 8 hourly.
- Symptoms of severe preeclampsia (headache, visual changes, retrosternal pain or pressure, shortness of breath, nausea and vomiting and epigastric pain) should be monitored at least every 8hrs.
- Presence of contractions, rupture of membranes, abdominal pain, or bleeding should be monitored.
- Laboratory testing (CBC, Platelet count, Liver enzyme, serum creatinine levels) daily or can be spaced to every other day if they remain stable and patient remain asymptomatic.

Fetal Assessment

- Kick count and NST
- Biophysical profile twice weekly
- Serial fetal growth every 2weeks and umbilical artery Doppler studies should be performed every 2weeks if FGR is suspected

Route of Delivery

Mode of delivery does not need to be cesarean delivery, Mode of delivery should be determined by fetal gestational age, fetal presentation, cervical status and maternal -fetal condition. Quality of evidence - Moderate. Strength of recommendation - Qualified. During labour measure BP hourly with mild to moderate hypertension and continually in severe hypertension. Continue use of antenatal antihypertensive treatment during labour. Limit maintenance fluid to 80ml / hour unless there are other ongoing fluid losses as hemorrhage. Determine the need for haematological and biochemical tests during labour using same criteria as in antenatal period. Do not routinely limit the duration of second stage of labour if BP is controlled with in target ranges. Recommend operative birth in second stage of labour for women with severe hypertension which has not responded to initial treatment²

Eclampsia: Presence of new onset grand mal seizures in a women with preeclampsia is defined as eclampsia. Eclampsia is preceded by a wide range of signs and symptoms, ranging from severe to absent or minimal hypertension, massive to no proteinuria and prominent to no edema. Clinical features which are potentially helpful in predicting impending eclampsia include

persistent occipital or frontal headaches, blurred vision, photophobia, Epigastric or right upper quadrant pain or both and altered mental status.

Magnesium sulfate is recommended for the control of seizures in eclampsia. Regimen used is intravenous loading dose of 4-6gm followed by maintenance dose of 1-2gm /hr or 10gm intramuscular along with I/V Bolus and 5gm I/M every 4hrly maintenance regimen for at least 24hrs. Woman should by monitored for Magsulf toxicity. Antihypertensive to be given for control of BP.Women with eclampsia should undergo delivery following stabilization.

Table 3: Antihypertensive agents used for urgent blood pressure control in pregnancy¹

Drug	Dose	Comments
Labetelol	10-20mg IV, then 20-80mg every 20-30min to a maximum of 300mg or Constant infusion 1-2mg/minIV	Considered a first line agent Tachycardia is less common and fewer adverse effects Contraindicated in patients with asthma, heart disease, or congestive heart failure
Hydralazine	5mgIV or IM. then 5-10mgIV every 20-40min Or Constant infusion 0.5-10mg/hr	Higher and frequent dosage associated with maternal hypotension, headache and fetal distress
Nifedipine	10-20mg orally, repeat in 30min if needed then 10-20mg every 2-6hrs	May observe reflex tachycardia and headaches

Table 4: Common oral antihypertensive agents in pregnancy¹

Drug	Dosage	Comments
Labetelol	200-2400mg/d orally in two or three divided doses	Well tolerated Potential bronchoconstrictive effect Avoid in patients with asthma and congestive heart failure
Nifedipine	30-120mg/d orally of slow release preparation	Donot use sublingual form
Methyldopa	0.5-3g/d orally in two to three divided doses	May not be as effective in control of severe hypertension
Thiazide diuretic	Depends on agent	Second line agent
ACE Inhibitors/ ARB	-	Associated with fetal anomalies. Contraindicated in pregnancy and preconception period

Women with Preeclampsia or eclampsia who require labour analgesia or anesthesia for cesarean delivery, the administration of neuraxial anesthesia (either spinal or epidural anesthesia) is recommended. Quality of evidence -Moderate, Strength of recommendation - Strong.

Postpartum Period

In women treated with antihypertensive drugs antenatally, continued antihypertensive treatment postpartum is recommended (Very-low-quality evidence. Strong recommendation). Treatment with antihypertensive drugs is recommended for severe postpartum hypertension¹⁰ (Very-low-quality evidence. Strong recommendation). It is suggested that BP to be monitored. For women with persistent postpartum hypertension BP of $\geq 150/100$ mm Hg, on at least two occasions 4-6hrs apart, Antihypertensive therapy is suggested. Avoid diuretic treatment if woman is breastfeeding or expressing milk. If the blood pressure is stable and well controlled, and there are no other features of severe disease women may be discharged. For the 1st week after blood pressure should be checked at least every other day, and then weekly. The antihypertensive medication can be reduced and then stopped when target blood pressures are achieved.

All women who have had a hypertensive complication in pregnancy should receive postnatal counseling regarding the management of future pregnancies. The risk of recurrence of preeclampsia is 2%-7%. For women with preeclampsia, the risk of recurrence is 16% if they delivered at term, 25% if they delivered before 34 weeks, and 55% if they delivered before 28 weeks¹¹. Women who have had preeclampsia and delivered before 34 weeks should be screened for antiphospholipid syndrome. All women who have had any element of hypertensive disease in pregnancy or the puerperium have an increased risk of cardiovascular disease in the future¹⁰.

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Calendar of Monthly Clinical Meetings 2018-19

Months	Name of the Institute
May, 2018	B L Kapur Hospital
June, 2018	Army Hospital - Research & Referral
July, 2018	AIIMS
August, 2018	VMMC & Safdarjung Hospital
September, 2018	Deen Dayal Upadhyay Hospital
October, 2018	ESI Hospital
November, 2018	MAMC & LN Hospital
December, 2018	Sir Ganga Ram Hospital
January, 2019	Dr RML Hospital
February, 2019	UCMS & GTB Hospital
March, 2019	LHMC
April, 2019	Apollo Hospital

Treating Non-Severe Hypertension (HT) in Pregnancy- Learning from the CHIPS trial and AHA



Dr Kanwal Gujral

Kanwal Gujral¹, Sakshi Nayar²

¹Co-Chairperson, Institute of Obstetrics and Gynaecology, Sir Ganga Ram Hospital, New Delhi

²Ex- Senior Resident, LHMC and SSK Hospital, New Delhi

Treatment of non-severe HT commonly referred to as mild to moderate HT in pregnancy has been a matter of debate. Several meta-analysis have suggested that lowering the blood pressure (BP) results in an increased risk of small for gestational age babies. A 10 mm fall in the mean arterial pressure results in a decrease of 176 grams in the birth weight¹⁻³. As a result of this evidence, majority of the obstetricians preferred not treating mild to moderate HT in pregnancy with anti-hypertensive medications.

The CHIPS Randomized Controlled Trial (Control of Hypertension in Pregnancy Study)⁴ was designed to study the effect of less tight versus tight control of HT on pregnancy complications which were

- Composite primary outcomes: miscarriage, ectopic pregnancy, termination of pregnancy, still birth, neonatal death or high level neonatal care for more than 48 hours until 28 days of life.
- Secondary outcomes: serious maternal complications - death, stroke, eclampsia, blindness, uncontrolled HT, pulmonary edema, myocardial ischemia, hepatic dysfunction, renal failure, blood transfusion occurring up to 6 weeks postpartum or until discharge whichever was later.

Nine hundred and eighty seven women with gestational age from 14 weeks 0 days till 33 weeks 6 days with non-proteinuric HT, pre-existing pregnancy or gestational HT (a diastolic BP [DBP] of 90-105 mmHg on no anti-hypertensive treatment or 85-105 mmHg on treatment) were recruited in the study. The women were randomly assigned to 1:1 ratio between a tight control group that is target DBP of 85 mmHg or a less tight control group that is a target DBP of 85-100 mmHg. Labetalol was the commonly used anti-hypertensive agent. Principle findings of the study were:

- A mean difference of 5.8 mmHg systolic BP (SBP) and 4.6 mmHg DBP between the two groups
- No difference in gestational age at delivery, birth weight < 10th centile and 3rd centile
- No difference in composite primary outcome rates. 31.4% less tight control and 30.7% tight control, adjusted odds ratio, 1.02; 95% confidence interval [CI], 0.77 to 1.35

- No difference in serious maternal complications. 3.7% less-tight control and 2.0% tight control, adjusted odds ratio, 1.74; 95% CI, 0.79 to 3.84
- A note worthy finding was difference in the incidence of severe HT, 40.6% with less tight control group and 27.5% in tight control group (P < 0.001)
- Also, less tight control group had higher association with low platelets and elevated liver enzymes although, not statistically significant.

The findings of CHIPS trial are consistent with other studies in terms of higher incidence of severe HT with less tight control group of BP⁵⁻⁷. Severe HT can lead to higher incidence of adverse maternal fetal outcome as indicated by some studies⁵⁻⁶ but not in the original CHIPS trial⁴.

A post-hoc analysis of CHIPS data⁸ using mixed effects and logistic regression model after adjustment of baseline factors was done and a comparison of outcomes according to severity of HT was analysed. 344 women who developed severe HT had following findings:

- Severe HT was associated with higher rates of each of CHIPS primary perinatal outcome - birth weight <10th centile, delivery at <34 or < 37 weeks, preeclampsia, preterm delivery, elevated liver enzyme (all P < 0.001), platelets < 100x10⁹/L (P = 0.006) and prolonged hospital stay (P=0.03).
- Notably adjustment for preeclampsia did not negate the relationship between severe HT and CHIPS primary outcome (P=0.001), birthweight < 10th centile (P=0.005) or elevated liver enzyme (P=0.02).
- The association between severe HT and serious maternal complication was seen only in less tight control group (P=0.02).

A very recent article from AHA⁹ has analysed the association between hypertensive disorders of pregnancy (HDP) and future cardiovascular diseases (CVD) in terms of subtype of HT, length, severity and treatment of HT in pregnancy. The adjusted ORs of admissions for future CVD for women with HDP as compared to women who remained normotensive were as follows

Future disease	Preeclampsia, OR (95% CI)	Gestational Hypertension, OR (95% CI)	All HDP, OR (95% CI)
Future hypertension	3.06 (2.18-4.29)	4.08 (3.23-5.10)	2.78 (2.47-3.13)
Ischemic heart disease	2.67 (1.49-4.81)	3.19 (2.11-4.83)	2.16 (1.98-3.84)
Stroke	2.03 (0.75-5.49)	0.57 (0.14-2.31)	1.94 (1.39-2.69)
Renal disease	4.74 (2.19-10.20)	3.45 (1.74-6.85)	2.76 (1.98-3.84)

A comparison of severity of BP and women who remained normotensive in their pregnancy and future cardiovascular admissions was as follows:

Future disease	Odds ratio	Adjusted odds ratio (for current age)	95% confidence interval	P value
Risk factor				
Future hypertension	5.78	5.82	4.47-7.58	<0.001
CVD				
Ischemic heart disease	4.05	3.91	2.46-6.23	<0.001
Stroke	2.73	2.65	1.16-6.04	0.020
Renal disease	4.83	4.66	2.25-9.62	<0.001

Also, use of antihypertensive medication was found to be beneficial in terms of maternal and neonatal outcomes but there was no significant difference for future admissions for any type of CVD between the women who received antihypertensives as against the women who did not.

Noteworthy was the fact that higher the level of HT in the pregnancy greater was the risk of future hypertension.

Putting together, the discussed three trials^{4,8,9} indicate -

- Severe HT in pregnancy leads to adverse fetal and maternal outcomes.
- Tight control of HT during pregnancy is associated with reduced frequency of severe HT.

- All HDPs are associated with risk of future CVD, greater the level of HT in pregnancy greater is the risk of future hypertension.

To conclude, the learning is - Treatment of mild to moderate hypertension in pregnancy with antihypertensive medication does make sense, especially in the background that there is no increased risk of adverse effect on the fetus.

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CONTROVERSY

Predictive Models for Severity of Preeclampsia - Clinical utility



Dr Ratna Biswas

Ratna Biswas

Director Professor, Department of Obstetrics and Gynaecology, Lady Hardinge Medical College & SSK Hospital, New Delhi

Preeclampsia and other hypertensive disorders in pregnancy remains a significant cause of maternal and fetal morbidity and mortality, globally. Severe maternal morbidities resulting from preeclampsia include eclampsia, cerebro-vascular accidents, pulmonary edema and renal failure. Presently, delivery is the only cure however, this is not always the best option for the fetus if the delivery occurs preterm. While expectant management has been proposed as a means to achieve improved fetal survival, it is unclear for how long to delay delivery and how high the resultant risk is for the mother. Precision in prognosis of women with preeclampsia is essential to support a practice of expectant management and guide decisions for timing of delivery.

Biomarkers and clinical parameters are the mainstay in determining the severity of disease. Understanding the pathogenesis is key to decoding the relation of the biomarkers with the onset and severity of disease. Many of the biomarkers used in predicting onset of preeclampsia is also crucial in forecasting the severity of disease.

Pathogenesis

Extravillous trophoblasts progressively invade the spiral arteries of the uterus in normal pregnancy during the first trimester of gestation. This results in development of low-resistance placental vessels which supply the fetus with adequate oxygen and nutrients. Growth factors belonging to the VEGF family are angiogenic in nature and cause vasodilation of uterine and myometrial arteries and is responsible for vascular remodeling during pregnancy.

Placental growth factor (PlGF) is a polypeptide and is a member of VEGF family responsible for development of low resistance vessels. The major source of PlGF is placental trophoblasts and it is expressed as several different isoforms like PlGF-1, PlGF-2, PlGF-3 and PlGF-4. It's a 30 KDa molecule that is freely filtered by the glomerulus, and hence it is found in the urine. A low concentration of PlGF in spot urine samples has been reported in preeclampsia.

Preeclampsia is characterized by defective placental angiogenesis. Trophoblast of women destined to develop preeclampsia overproduces two anti-angiogenic peptides that enter the maternal circulation. These are:

1. Soluble Fms-like tyrosine kinase 1 (sFlt-1). It is a truncated splice variant of the membrane-bound Flt-1. It circulates freely in the serum, where it binds and neutralizes VEGF and PlGF. Several studies have demonstrated the association between increased sFlt-1 levels and preeclampsia.
2. Soluble endoglin (sEng) is a potential anti-angiogenic factor which interferes with binding of TGF β 1 to its receptor and thereby affects production of nitric oxide, vasodilation and capillary formation by endothelial cells in vitro. In normal pregnancy, levels of sEng in serum fall between first and second trimesters. However, it has been reported that sEng is elevated in second-trimester maternal serum in patients who are destined to develop severe preeclampsia.

Placental hypoxic-ischemia in preeclampsia up-regulate soluble anti-angiogenic factors (soluble fms tyrosine kinase-1) which sequesters VEGF and PlGF thereby resulting into decreased free VEGF and PlGF levels and hence endothelial dysfunction and vasoconstriction. Thus, reduced PlGF levels are found in preeclampsia and might be related with the adverse fetomaternal outcomes like eclampsia, placental abruption, renal failure, pulmonary edema, fetal hypoxia, elevated liver enzymes, low platelet levels, intracranial bleed, hypertensive crisis, maternal or fetal mortality.

Predictive Models of Severe Preeclampsia

Placental Growth Factor (PlGF) (Alere Platform)

It is one of several biomarkers which have been shown to have a predictive capacity for the screening and detection of pre-eclampsia. PlGF is produced by the syncytiotrophoblast and is identifiable in maternal blood from as early as 12 weeks with concentrations increasing with gestation until around 30 weeks before declining until birth. A decline in PlGF appears to represent a negative syncytiotrophoblast stress response to a variety of insults ranging from hypoxia, inflammation, oxidative stress and is also seen as part of syncytiotrophoblast aging. PlGF concentrations are lower in pre-eclampsia, and extremely low in severe early-onset pre-eclampsia. Recently it has also been suggested that low PlGF concentrations are associated

with fetal growth restriction (FGR) and placental dysfunction.¹

Currently the National Institute for Health and Care Excellence (NICE) recommends the use of two platforms for PlGF assessment in pregnancy, produced by Alere and Roche.

The Alere platform uses antibodies against PlGF isoform-1, with some cross-reactivity for isoform-2, and has a moderate body of evidence for its clinical effectiveness at determining pre-eclampsia requiring delivery within 14 days. The results are further categorised by PlGF concentration: i) very low (<12 pg/ml), ii) low (12-100 pg/ml), iii) normal (>100 pg/ml).

MAPPLE study evaluated 396 women managed with revealed PlGF and compared it with 287 women with concealed PlGF (PELICAN study). The objective of the MAPPLE study was to report clinical outcomes in women managed with revealed PlGF results and to compare those outcomes with those of the PELICAN study in which clinicians were not informed of the PlGF result. This would identify the potential clinical implications of revealing PlGF results to the clinician.

Revealed PlGF led to delivery 1.4 weeks earlier (-2.0 to -0.9, 34.9 weeks vs 36.7 weeks). There was no increase in obstetric intervention. A very low PlGF (<12 pg/ml) was universally associated with a poor pregnancy outcomes. Revealed PlGF led to fewer perinatal deaths (2 vs 9; RR 0.16, 95% CI 0.03-0.74) and fewer babies with birthweight <3rd centile (28.9% vs 36.1%; RR 0.80, 0.65-0.99) but with more neonatal adverse outcomes (30.4% vs 17.1%; RR 1.78, 95% CI 1.32-2.41). Respiratory morbidity like respiratory distress syndrome and bronchopulmonary hypoplasia was the prime adverse neonatal outcomes. Triaging PlGF based management thus would reduce the serious adverse fetal outcomes but at the expense of increased respiratory morbidity.

In a study by Ormisher E it was concluded that in women with pre-existing hypertension, PlGF was a useful adjunct to standard care. PlGF had a significant impact on scan surveillance, maternal surveillance and very few women with PlGF <12 pg/ml continued >14 days; However low PlGF should not always trigger delivery.¹

Soluble FMS-LIKE Tyrosine Kinase 1 (sFlt1) Relative to PlGF (The Roche Platform)

The sFlt-1/PlGF ratio also has a developing body of evidence (PROGNOSIS study). Both tests have been endorsed by NICE for the investigation of hypertension in pregnancy, to 'rule out' a diagnosis of pre-eclampsia.

In the Angiogenic profile in the Finnish Genetics of Pre-Eclampsia Consortium (Finnpac) Cohort it was observed that the proportion of women exceeding all cut-offs of the sFlt-1/PlGF ratio (≥ 33 , ≥ 38 , ≥ 85 and ≥ 110) was

greater in the PE group, but there were also pre-eclamptic women who met rule-out cut-off or did not meet rule-in cut-off. It was concluded that primiparous pregnancies have more anti-angiogenic profile during second/third trimester compared with multiparous pregnancies. It also suggested that certain maternal characteristics, e.g. BMI, smoking and pre-existing diseases, should be taken into account when considering different sFlt-1/PlGF cut off ratios².

The FullPIERS (Pre-Eclampsia Integrated Estimate of Risk) Model

This was developed to predict adverse maternal outcomes resulting from pre-eclampsia. The study's primary adverse maternal outcome was defined as one or more of the pre-specified severe maternal complications, which included central nervous system (CNS), hepatic, renal, cardiovascular and respiratory outcomes, occurring within 48 hours of a woman's admission for pre-eclampsia. The multivariable model was developed in 2010 using a cohort of 2023 women admitted in tertiary centres in high income countries (HICs) with a 5% rate of adverse maternal outcomes. Six predictor variables were included in the model: gestational age, chest pain or dyspnoea, oxygen saturation (SpO₂), platelet count, serum creatinine, and serum aspartate transaminase. The model had good discrimination, with an area under the receiver operating characteristic curve of 0.80 (95% confidence interval, 0.75-0.86), and a calibration slope of 0.68.³

FullPIERS Calculator

Gestational age (at delivery, if *de novo* postpartum pre-eclampsia) :

 weeks days

Did the patient have chest pain or dyspnoea?

SpO₂* (use 97% if unknown):

 %

Platelets (x10⁹/L):

Creatinine (μmol/L):

Switch To Imperial Units

AST/SGOT (U/L):

CALCULATE

Probability of adverse maternal outcomes:

%

The estimated likelihood ratio at the predicted probability of $\geq 30\%$ was 23.4 (95% confidence interval, 14.83-36.79), suggesting a strong evidence to rule in adverse maternal outcomes. The fullPIERS model will aid in identifying women admitted with early-onset preeclampsia in similar settings who are at the highest risk of adverse outcomes, thereby allowing timely and effective interventions.

A study to integrate placental growth factor (PIGF) into fullPIERS model is underway, where both PIGF and fullPIERS will be used to risk stratify women with pre-eclampsia.

The miniPIERS: Pre-Eclampsia Integrated Estimate of Risk

Women in low- and middle-income countries (LMICs) are more likely to develop complications of pre-eclampsia than women in high-income countries and most of the deaths associated with hypertensive disorders of pregnancy occur in LMICs. The high burden of illness and death in LMICs is thought to be primarily due to delays in triage (the identification of women who are or may become severely ill and who need specialist care) and delays in transporting these women to facilities where they can receive appropriate care. Because there is a shortage of health care workers who are adequately trained in the triage of suspected cases of hypertensive disorders of pregnancy in many LMICs, one way to improve the situation might be to design a simple tool to identify women at increased risk of complications or death from hypertensive disorders of pregnancy. Here, the researchers develop miniPIERS (Pre-eclampsia Integrated Estimate of Risk), a clinical risk prediction model for adverse outcomes among women with hypertensive disorders of pregnancy suitable for use in community and primary health care facilities in LMICs. The miniPIERS model included parity (whether the woman had been pregnant before), gestational age (length of pregnancy), headache/visual disturbances, chest pain/shortness of breath, vaginal bleeding with abdominal pain, systolic blood pressure, and proteinuria detected using a dipstick. The model was well-calibrated (the predicted risk of adverse outcomes agreed with the observed risk of adverse outcomes among the study participants), it had a good discriminatory ability (it could separate women who had an adverse outcome from those who did not), and it designated women as being at high risk (25% or greater probability of an adverse outcome) with an accuracy of 85.5%. Importantly, external validation using data collected in fullPIERS, a study that developed a more complex clinical prediction model based on data from

women attending tertiary hospitals in high-income countries, confirmed the predictive performance of miniPIERS⁴

miniPIERS CALCULATOR

Gestational age at admission:

weeks days

Any previous deliveries >20weeks gestation?

Chest pain and/or dyspnoea?

Headache and/or visual changes?

Vaginal bleeding with abdominal pain?

Systolic BP* (mmHg):

Dipstick proteinuria:

SpO2 (Optional):

%

CALCULATE

Probability of adverse maternal outcomes*:

%

*Risk should be calculated only for women with hypertension.

Cell-Free Fetal Hemoglobin, Heme & Hemopexin (HPX): Potential biomarkers

Hemolysis and the subsequent release of cell-free Hb and heme occur in a wide range of clinical conditions like preclampsia. The release of cell-free Hb and heme causes a range of pathophysiological effects where hemodynamic instability and tissue injury constitutes the major insults. Immediate effects include scavenging of the potent vasodilator nitric oxide (NO) that leads to increased arterial blood pressure. Furthermore, cell-free Hb and free heme accumulates within the renal vascular wall causing subsequent organ failure. Long-term exposure to cell-free Hb and heme has been described to be associated with NO depletion, inflammation and oxidative stress. Thus, inadequate scavenging and

protection against extracellular Hb and its metabolites during pregnancy may cause fundamental damage to the vascular bed. In fact, the long-term effects of PE are increased risk of cardiovascular disease and stroke later in life. The importance of cell-free HbF and its downstream metabolites free heme and ROS, in the development of PE-related damage and symptoms, have been described.

Protective mechanism against extracellular Hb and free heme includes several Hb- and heme-detoxification systems. Previous studies have shown that the plasma levels of hepatoglobin (Hp) are decreased in PE pregnancies. If Hp becomes depleted, as a consequence of consumption due to high levels of cell-free Hb or prolonged exposure time to cell-free Hb, the uncleared oxyHb will undergo auto-oxidation reactions resulting in the formation of metHb, freeheme and ROS. Furthermore, the non-Hp bound Hb will be accumulated within organs.

Studies have shown that enzymatically active Hemopexin (Hpx) can affect the renin-angiotensin system (RAS) in vitro by downregulating the vascular angiotensin II receptor (AT) and promoting an expanded vascular bed. It could be speculated that increased heme levels, resulting from elevated levels of cell-free Hb in women with PE leads to a consumption of Hpx and consequently a reduced Hpx activity, resulting in an enhanced AT receptor expression and a contracted vascular bed. This, together with NO consumption, may be important blood pressure regulating effects caused by elevated extracellular HbF observed in PE. Hemopexin (Hpx) concentration has shown a significant negative correlation to the blood pressure. It could be speculated that this is also correlated to the severity of the disease, although no statistical significance was seen between Hpx and blood pressure when separating PE patients from controls⁵.

Proteinuria - Podocyturia: Markers Of Renal Injury

Renal involvement is often interpreted in the context of endothelial dysfunction, which is believed to be the central pathophysiologic mechanism that underlies multiorgan involvement in preeclampsia. Endothelial dysfunction may occur, in part, as a consequence of the imbalance between circulating proangiogenic and antiangiogenic factors in favor of the latter, resulting in decreased levels of vascular endothelial growth factor and placental growth factor. At the kidney level, podocyte-specific heterozygosity for vascular endothelial growth factor-A results in renal disease in mice by 2.5 weeks of age and is characterized by proteinuria and endotheliosis. It remains unclear as to how endothelial dysfunction causes dysregulation of podocytes (terminally differentiated glomerular

epithelial cells that cannot divide), which play a crucial role in maintaining the selective permeability of the glomerular capillary wall.

A recent report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy made major changes with respect to the diagnostic value of renal involvement in preeclampsia by eliminating the dependence of a preeclampsia diagnosis solely on proteinuria. In the absence of proteinuria, preeclampsia is confirmed when hypertension is associated with any of the following: thrombocytopenia, elevated liver function test results, AKI, pulmonary edema, or new onset of cerebral/visual disturbances. The controversy surrounding the usefulness of proteinuria in diagnosing preeclampsia may be due, at least in part, to the fact that proteinuria may be a late marker of renal injury and that studies of early, subclinical markers of renal injury are needed⁶.

Spot urinary protein to creatinine ratio can be used as an alternative to 24 hour urinary protein because urinary creatinine in an individual is constant throughout the day and the ratio reflects protein excretion. Additionally protein creatinine ratio corrects for variation in urinary concentration due to hydration as both protein and creatinine are highly soluble and are similarly affected by dilution. International society for the study of hypertension in pregnancy proposed the use of spot PCR as an alternative to 24 hour urinary protein. The recommended threshold for significant proteinuria (more than 0.3 gm/day) was 30 mg/mol (0.27gm per gm creatinine). It can be quantified and has shown a positive correlation with severity of disease and adverse outcome.

In addition other markers of renal injury are under evaluation. Evidence has emerged indicating that either structural podocyte injury, as evidenced by downregulation of podocyte-associated proteins, or urinary loss of viable podocytes (*i.e.*, podocyturia) may play a central role in the renal involvement observed in preeclampsia.

Prediction of adverse outcome in preeclampsia especially the serious adverse outcome is a step forward to reduce the maternal mortality and serious maternal morbidity. The PLGF based triaging, sFlt-1/PlGF ratio, FULLPIERS and miniPIER models are established and well validated models and have a definite role in stratification of disease severity and triaging management.

Cell-free fetal hemoglobin, heme, hemopexin and markers of renal injury like podocyturia and urinary protein creatinine ratio may have a role but controversy remains in their clinical utility. Large scale multicentric trials are needed to quantify these variables for risk prediction and establish their role in the clinical management of preeclampsia.

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All interested AOGD members working in the field may contact the concerned chairperson to become members of respective sub-committees. All AOGD members can become members of maximum two sub-committees.

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Reproductive Endocrinology Committee	Dr Nalini Mahajan	9810087666	dr.nalinimahajan@gmail.com

CASE APPROACH

Neurological Symptoms in Patient with Preeclampsia



Dr Swati Agrawal

Swati Agrawal¹, Gargi Agarwal²

¹Associate Professor, ²Senior Resident, Department of Obstetrics & Gynaecology, LPMC & SSK Hospital, New Delhi

Introduction

Preeclampsia accounts for significant morbidity and mortality in pregnant women throughout the world. Neurological complications, arising consequent to eclampsia, cerebrovascular accidents and cerebral edema, are responsible for upto 75% of mortality in these women.¹ Prompt diagnosis and aggressive management of neurological symptoms in patients with preeclampsia may avert these complications and improve the patient outcome. It is therefore imperative for all obstetricians to be familiar with the workup and management of such patients.

Cerebral Hemodynamics in Preeclampsia

Many studies employing transcranial doppler ultrasound demonstrate significantly increased cerebral blood flow in women with severe preeclampsia as compared to normotensive pregnant controls.² Endothelial dysfunction and impaired cerebral autoregulation are proposed to be the key factors for the development of cerebral abnormalities associated with preeclampsia and eclampsia.¹ In response to sudden elevations in systemic blood pressure, cerebral “overregulation” may lead to vasospasm and diminished cerebral blood flow. This may result in cytotoxic edema, ischemia and eventually tissue infarction.³ An alternative concept suggests that acute severe hypertension exceeds the cerebral autoregulatory capacity leading to increased hydrostatic pressure, hyperperfusion and extravasation of plasma and red cells with resultant vasogenic edema.⁴

Clinical Presentation and Workup

The various neurological symptoms in a preeclamptic patient include tonic clonic seizures, paresthesias, hemiparesis / quadriparesis, headache / visual disturbances, blindness, speech disturbances, ataxia, altered state of or loss of consciousness and coma.

All preeclamptic patients presenting with seizures should prompt the clinician to conduct a thorough neurological examination. History of preexisting neurological disorders such as epilepsy should be sought. As eclampsia will account for seizures in most of the cases, neurological imaging should be reserved for patients having additional focal neurological signs,

atypical or recurrent convulsions, prolonged loss of consciousness and those having delayed recovery.⁵

Magnetic resonance imaging (MRI) has a superior soft tissue contrast and multiplanes resolution compared with computed tomography (CT) and is thus considered to be the preferred neuroimaging modality. MRI can effectively diagnose not only haemorrhage but ischemia and edema in patients with preeclampsia.⁶

Other investigations include blood tests like a complete hemogram, liver and kidney function tests to diagnose complications like HELLP. Blood sugar and serum electrolytes may help in diagnosing non-neurological conditions which can manifest with neurological symptoms such as altered sensorium due to dyselectrolymia.

Patients presenting with visual symptoms such as scotomia, blurred vision, diplopia, chromatopsis, homonymous hemianopia or blindness should undergo detailed ophthalmological examination. An ophthalmologic examination may also help to detect optic disc edema consequent to raised intracranial pressure. Normal ophthalmological examination with intact pupillary light reflex and ocular movements is characteristic of cortical blindness. Cortical blindness results due to focal cerebral edema and is usually transient.

Differential Diagnosis

The various differential diagnoses for a preeclampsia patient presenting with neurological symptoms are as follows:-

Posterior Reversible Encephalopathy Syndrome(PRES)

PRES, also known as reversible posterior leukoencephalopathy syndrome (RPLS), is a rare clinico-neurological entity characterised by headache, confusion, visual disturbances or blindness and seizures. It most commonly occurs in patients with preeclampsia and eclampsia but may appear in other clinical settings such as acute or chronic renal disease, use of cytotoxic drugs, autoimmune disorders and electrolyte disturbances.⁷

The diagnosis is established by documenting symmetrical white matter edema in the posterior cerebral hemispheres that particularly involve the

parieto-occipital regions bilaterally. Treatment includes prompt control of malignant hypertension to lower the diastolic pressure to about 100 to 105 mm Hg. More aggressive blood pressure control is avoided to prevent loss of cerebral autoregulation with resultant cerebral ischemia. Use of parenteral magnesium sulphate for the prevention and treatment of seizures is recommended.

PRES syndrome is usually reversible if recognized and treated promptly but spontaneous recovery is not the rule. Hence it is suggested that “reversible” could be a misleading term and “potentially reversible encephalopathy syndrome” could be more apt nomenclature for this entity. Many studies have demonstrated that upto one fourth of eclamptic women may show evidence of cerebral tissue loss and impaired cognitive functioning even months after delivery.⁸ However data about long term neuro-cognitive consequences of PRES in postpartum patients is lacking.

Cerebrovascular Accidents

Hypertensive intracerebral hemorrhage in preeclamptic patients is more common in older women with underline chronic hypertension. The cause is attributed to long standing hypertension induced lipo hyalinosis affecting small cerebral arteries. The sites most commonly affected are the striatocapsular area, thalamus, cerebellum and brainstem. Patients with complications such as HELLP and coagulopathy are also at an increased risk for developing this complication. Very rarely, intracranial hemorrhage may occur in patients with preeclampsia due to a ruptured aneurysm or arteriovenous malformation. The neurological manifestations vary from sudden severe headache, seizures, vomiting, paresis, confusion, paresthesia, visual and speech disturbances to loss of consciousness and coma.

Subarachnoid hemorrhage is infrequently reported in preeclampsia and has a benign prognosis.

Neuroimaging studies remain the gold standard for diagnosis of this condition. Intracranial hemorrhage usually leads to maternal death or major permanent disability.

There are no reliable means to predict the occurrence of this catastrophic event in preeclamptic women and prevention seems to be the only way to prevent morbidity and mortality. Proper control of blood pressure, timely treatment with magnesium sulphate and maintaining adequate platelet levels to avoid haemorrhage, is thus of paramount importance in patients with severe preeclampsia and eclampsia.

ACOG, Canadian & NICE Guidelines all recommend immediate antihypertensive therapy for blood pressures consistently equal to or greater than a systolic of 160 mmHg and/or diastolic of 110 mmHg [mean arterial pressure (MAP) of around 130 mmHg].⁹ However, many

patients may sustain an intracerebral bleed at MAPs less than 130 mmHg suggesting that rapidity of change in blood pressure and the absolute level of systolic blood pressure, may be more clinically relevant.¹⁰ Intravenous labetalol and hydralazine are the recommended first line therapies for acute severe hypertension but immediate release oral nifedepine may be given where i.v. access is not available. Treatment with first line antihypertensives should be given within 30-60 minutes of confirmed severe hypertension to reduce the risk of cerebrovascular accidents.⁹

In patients with HELLP syndrome, correction of platelet numbers and coagulation defects is important before delivery, cesarean section or any other surgical intervention. This includes the correction of a coagulopathy with fresh frozen plasma and/or cryoprecipitate and a platelet transfusion to correct the platelet count. The American Society of Hematology recommends a minimum platelet count of $50 \times 10^9/L$ prior to labour and delivery ;and a platelet count of more than or equal to $80 \times 10^9/L$ before regional anaesthesia.¹¹ After delivery, if the platelet count is above $40 \times 10^9/L$, a significant postpartum haemorrhage or spontaneous bleeding is unlikely and in the absence of haemorrhage repeated platelet transfusions are not advocated unless counts fall below $20 \times 10^9/L$.¹²

Other Differentials

If the neurological imaging fails to reveal any of the above two diagnosis, other conditions which may be unrelated to preeclampsia should be considered for the diagnosis of persistent neurological symptoms in these patients. These conditions include tubercular meningitis, multiple sclerosis, Guillain barre syndrome, disseminated toxoplasmosis, A-V malformation, cerebral carcinoma, cerebral venous thrombosis and non-neurological conditions such as Bartter syndrome causing seizures due to dyselectrolytemia. In this regard, it also becomes pertinent to mention magnesium toxicity as an important cause of neuromuscular weakness and confusion in patients of severe preeclampsia and eclampsia. In these patients too, the neurological imaging will fail to reveal anything but getting serum magnesium levels will clinch the diagnosis.

Conclusion

Neurological symptoms in patients with preeclampsia call for an urgent and thorough neurological review. These symptoms are usually consequent to complications of preeclampsia and eclampsia. However, it is essential to exclude preexisting neurological disorders as well as any other systemic illness by a detailed history and meticulous examination.

Neuroimaging tools like CT and MRI are the mainstay for making a definitive diagnosis. Prompt diagnosis and

effective control of blood pressure can improve the outcome and prevent permanent neurological disability in these patients.

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Congratulations to AOGD Members on their Achievements at North Zone Yuva FOGSI 2018

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- North Zone Yuva FOGSI: Organizing Chairperson- Dr Pratima Mittal, Co-ordinator- Dr Achla Batra
- Dr Abha Singh organizing chairperson for workshop on cesarean skills.
- Dr Sharda Jain felicitated as the Woman Achiever of the year by the Public Awareness Committee, FOGSI.
- Dr Shashi Prateek awarded with "Unsung Hero" award by FOGSI.
- Dr Meenakshi Ahuja awarded for creating Public Awareness.
- Dr Kavita Aggarwal, Assistant Professor, SJH, delivered the Kamini Rao Yuva FOGSI Oration.
- Dr Neha Gupta, Associate Professor, HIMSR, awarded Yuva Achiever prize.
- Dr Bindiya Gupta, Assistant Professor, GTBH, awarded Yuva Achiever runnerup prize.
- Dr Vaishnavi Schhan, SJH, awarded first prize in oral Gynae paper presentation.
- Dr Aakriti Batra, Santosh Hospital, Ghaziabad awarded second prize in poster presentation.
- SJH team led by Dr Shubham awarded the best street skit on quality and ethics.

Sailing through Turbulent Times

Mohit D Gupta

Professor of Cardiology, GB Pant Institute of Postgraduate Medical Education and Research



Dr Mohit D Gupta

If at any point of your life: you feel irritated, lonely, frustrated, angry, desperate and want to run away: Go ahead and read it.

When you reconnect with yourself, nature and the supremepower, the ways to manage your stress naturally appear.

Present day life is more than a computerised and mechanised life. It has given us the joy of best technical facilities, medical facilities, equipments and facilities that are just a click away, but the joy of BEING is far away from us. We as human beings have learned the art earning but lost the true art of living in our life.

It may be apt to say that today.

We are no more Human Beings: but we have transformed ourselves into HUMAN DOINGS.

Did you know every 2 seconds, 7 people die of stress related illnesses around the world? That's 110 million people every single year, all being wiped off this planet thanks to a everyday trending word called #stress. When we talk about global and national statistics: India is going to be on the top when talked about for diseases like Diabetes and Hypertension. It is predicted that by 2020, 80% of the world population will not be able to

have comfortable sleep and will suffer from some or the other form of depression. So, despite technological advancements, degradation of values and moral system has led to significant unrest in the society and the world at large.

One of the things that concerns us about this statistic is that more often than not, it isn't those really big unavoidable stressful events in life that contribute most here, rather the build-up of all the little stresses and frustrations every single day. Over a span of many years this adds up and take a toll on their health. Accumulation of repeated negative and stressful incidents depletes our mindpower. This leads to erratic and hasty thinking, missing options and perspectives, and since we are unable to find a solution to this problem immediately, we then end up just going around in circles, only making ourselves more stressed in the process.

Numerous common stressors that we all face are seen below:

We must understand that in the center of this cycle are WE. Since we are negatively impacted, hence the change has to be brought by us and that too from within. The situations and people will never change the way we want.



In this series: We will examine, understand and practice simple tips to easily get rid of stress and negativity from our mind and create a beautiful life. I will suggest a few doable exercises for all that can really make a great difference in our life: BUT practice is the key.

1. Breaking the cycle: we have created a routine for ourselves in such a way that we don't find time for our own selves. We need to break this cycle wherever possible. Understanding that first step to relieve ourselves is TAKE OUT TIME. Are we ready?

Practice: Get rid of the word BUSY: This depletes energy. Instead use the word BE EASY: we are easy inside, we may be busy outside. Use this for 1 month and you will find your energy levels automatically increasing.

2. Finding Quiet: God talks when we listen. But it's more like a whisper than a shout. Find quiet so you can hear.

Practice: Let us do this exercise: 10 minutes in the morning when we get up: sit in silent initiate your communication with God, contemplation of thoughts, concentration and self-actualisation with supreme. Give yourself powerful thoughts that today is a great day: I am going to make myself and everyone happy, because I am the embodiment for purity, peace and happiness. Similarly, 10 minutes in the night before going to sleep: sit in silence: listening to some good music and reading something that enlightens your mind. This is important because whatever we read in the night before going to sleep; the state of our mind will be same during sleep. If we read positive and constructive things our mind is peaceful and we will have quality sleep.

3. Remember what you enjoy and love to do: The most important person in your life is YOU. It is important that we take out time for our ourselves. Doing small little things that bring joy and pleasure to me must be integrated in my routine. This may include exercise, sports, cooking, music, playing with children, reading or whatever. Out of 24 hours in a day: I must take out time to do what I love the most. That charges me and gives me sense of happiness and joy.

Practice: Life may be demanding: but today I take out few moments to do what I love the most.

4. Be Grateful: We should be thankful and express gratitude to everyone whom we meet. Everyone we meet in our life is because of a reason. Good people teach us what to do and rest teach us to be patient and what is to be avoided. WE LEARN EITHER WAY. So we must be thankful to one and all.

Practice: Let us practice gratitude towards everyone we are meeting. Be thankful in your personal, social and professional life and you will see negativity and waste fly away from you.

We feel stressed when we take on the world as a human and try to put our will against it. When we give in to our inability to use our will, and empower ourselves with power from almighty, our struggle naturally ceases

Let us practise these small exercises in our life and see what difference is created. In the next article; we will reflect on some more facts that will keep us happy and enlightened.

Wishing you a Happy and Peaceful Life!



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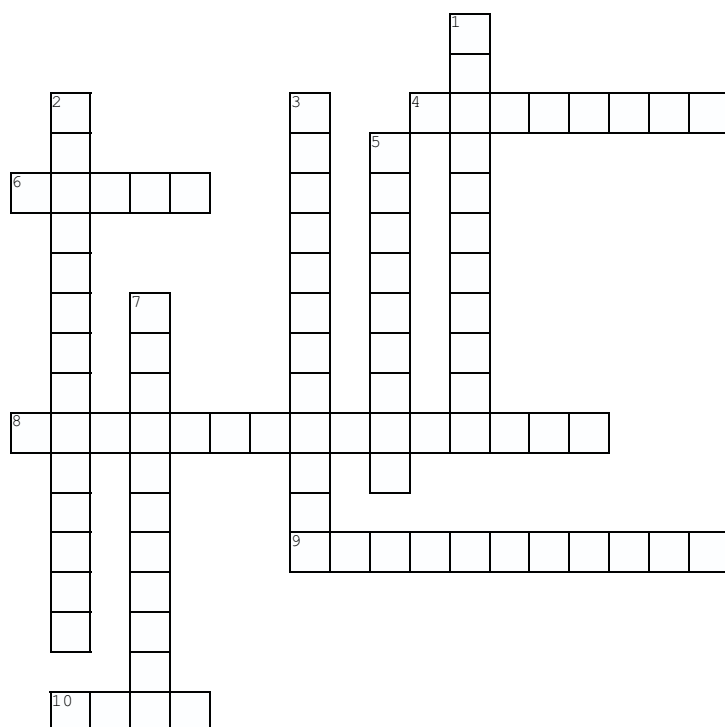
The Maze of Knowledge

Swati Agrawal

Associate Professor, Department of Obs & Gynae, LHMC & SSK Hospital, New Delhi



Dr Swati Agrawal



Down

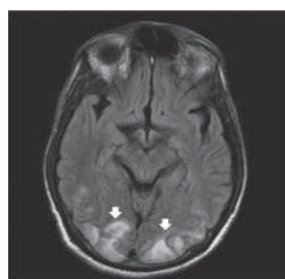
1. Natural insulin sensitizer used in PCOS patients
2. Another name for polycystic ovarian syndrome
3. Steroidal progestin used in OCPs reported to pose increased risk for venous thromboembolic events than conventional OCPs
5. Criteria used for diagnosis of PCOS
7. Drug used for treatment of acute severe hypertension

Across

4. Transient blindness caused due to focal cerebral edema in preeclampsia
6. Serious complication of preeclampsia characterized by hemolysis
8. Scoring system for evaluation & quantification of hirsutism
9. Key dysfunction in pathophysiology of preeclampsia
10. A potentially reversible neurological complication in preeclampsia

PICTORIAL QUIZ

A Picture is Worth a Thousand Words



- Q1. What does the above MRI picture show?
- Q2. What is the diagnosis?
- Q3. How will this patient present?
- Q4. What is the management?



- Q1. What condition does the above picture show?
- Q2. What is the chief underlying cause?
- Q3. List 2 disorders which may present with the above condition?
- Q4. Mention cosmetic treatment options for severe cases?

*Whatsapp your answers to 9953938995 with your name and designation.
The names of first correct 3 entries will be acknowledged in our next bulletin.*



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Events Held

April 2018

- On occasion of "World Health Day" talk on "Healing the Healers" by Dr Mohit Gupta, Professor of Cardiology GB Pant Hospital, on 12th April, 2018 at the Swarn Jayanti Auditorium, LHMC.



- CME under aegis of "Breast and Cervical Cancer Awareness Prevention and Screening Subcommittee" of AOGD being organized by Dr. Anita Sabharwal on 13th April 2018.



- Urogynaecology Live Workshop under the aegis of AOGD on 15th of April 2018 at Sunderlal Jain Hospital



- AOGD Monthly Clinical Meeting on Monday, 23rd April 2018 at Apollo Hospital, Sarita Vihar



- CME on PCOS organised at Deen Dayal Upadhyay Hospital under the aegis of Adolescent Sub-Committee of AOGD on 24th April 2018.



- Dr Abha Singh President AOGD and Dr Kiran Aggarwal Secretary AOGD attended the Management Committee Meeting at North Zone Yuva FOGSI, Dehradun 28th & 29th April, 2018.



- Dr Sharda Jain receiving award of “Women Achiever of the Year” at North Zone Yuva FOGSI, Dehradun 28th & 29th April, 2018.



March 2018

- CME on Screening and Prevention of Cervical Cancer under the aegis of AOGD on 27th March, 2018 at Sir Ganga Ram Hospital.





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Highlights

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- TLH made easy - with different vessel sealers
- Large Uterus/ Scarred Abdomen/ Endometriosis
- Changing Trends in Laparoscopic Onco Surgeries
- Advancement in Urogynaecology
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Obituary

Dr. V. Hingorani



Dr. Prof Vera Hingorani, 94 years, left for her heavenly abode on 23rd April 2018 at Houston. “Dr. Hingorani was born to Shri. Tecklaand Hotchand and Smt. Lilawati on 23rd December 1924 at Bubak in India. She graduated in medicine from Lady Hardinge Medical College in 1947. After specialising in Gynecology and Obstetrics, she joined the All India Institute of Medical Sciences, New Delhi in 1959 and rose in ranks to head the Department of Obstetrics & Gynecology, a post she held till 1986. She was also a former honorary gynaecologist and obstetrician to Mrs. Indira Gandhi, and Mrs. Pratibha Patil, the former president of India. The Government of India awarded her the fourth highest Indian civilian honour of Padma Shri in 1984. After superannuation from the AIIMS, she joined Batra Hospital and Medical Research Centre in 1987, worked there till 1996 and returned to AIIMS in 1997 to work as a consultant.

Dr. Hingorani was a former clinical director at the World Health Organization and had written several articles and medical papers in Obstetrics & Gynecology. She was an honorary fellow of the American Congress of Obstetricians and Gynecologists and an elected fellow of the National Academy of Medical Sciences. Dr. Hingorani was involved with Operation ASHA, a non governmental organization working for eradicating tuberculosis from India, as a member of their management team.

The Association of Obstetricians and Gynaecologists of Delhi mourns the departure of Dr. Prof. Vera Hingorani, a stalwart and an academician-par excellence. May her soul rest in peace.

Dr. Manpreet Gambhir

Dr. Manpreet Gambhir, Husband of Dr. Neena Malhotra, Professor, Dept of Obstetrics & Gynecology, AIIMS had an untimely demise on 16th April 2018. The AOGD fraternity stands by Dr. Neena in this time of grief and extends its condolences. May god give her and the family strength to bear the irreparable loss.

Mr. Akhil Chadha

Mr. Akhil Chadha, son of Gynaecologist & AOGD member Dr. Geeta Chadha, Indrapratha Apollo Hospital, and Mr. Sunil Chadha, met with a tragic end at a tender age of 31 years on 10th April 2018. The AOGD fraternity extends its heartfelt condolences to the bereaved family. May God give them the strength to bear this irreparable loss.

Shri Man Mohan Buckshee

Shri Man Mohan Buckshee, husband of our patron Profesor Kamal Buckshee, Ex-Head of the Department, AIIMS & Ex- President FOGSI left for his heavenly abode on 3rd May 2018. The AOGD fraternity extends its heartfelt condolences to Madam Buckhsee and family.

Standards of Care in Diagnosis and Management of Adolescent PCOS



Dr Pikee Saxena

Pikee Saxena¹, Manmeet Kaur²¹Professor, ²Senior Resident, Department of Obstetrics & Gynaecology, Lady Hardinge Medical College & SSK Hospital, New Delhi

Introduction

Prevalence of PCOS in India varies from 3.7% to 22.5%^{1,2} and in the adolescent group it ranges from 9.13% to 36%^{3,4}. Increase in the magnitude of adolescent PCOS is due to lack of physical activity, faulty dietary habits, environmental issues and excessive stress in the competitive world. PCOS during adolescence may be the earliest manifestation of the metabolic syndrome resulting in obesity, gestational diabetes mellitus, hypertension, type 2 diabetes mellitus, dyslipidaemia, coronary artery disease or endometrial hyperplasia and malignancy in later life. Therefore, early identification of PCOS during adolescence may have important implications in preventing long term sequelae.

Pathophysiology

Potential factors involved in pathophysiology of PCOS involve disturbances in steroidogenesis, ovarian follicular maturation, neuroendocrine function, metabolism, insulin secretion and sensitivity, adipose cell function, inflammatory factors, and sympathetic nerve function. Combination of different factors may be involved in individual patients. Environment factors such as food choice, exercise, and endocrine disruptors influence the development of clinical features. Genome-wide association studies have identified loci of interest in close proximity to genes involved in gonadotropin secretion, gonadotropin action, ovarian follicular development, and insulin sensitivity⁵

High Risk Factors for Development of PCOS

It has been observed that intrauterine exposure to androgen excess may predispose a female fetus to

PCOS. Babies born with intrauterine growth retardation and also with macrosomia are at high risk of developing PCOS.

It is recommended that adolescents showing at least one biochemical and one clinical feature should be followed up closely for likelihood of PCOS⁶.

1. *Biochemical characteristics*: High BMI > 97.5th percentile for age in adolescents, insulin resistance, family history of diabetes, PCOS, obesity or any other marker of dyslipidaemia (elevated serum total cholesterol, triglyceride and LDL-C levels).
2. *Clinical symptoms*: Pubertal deviations (early or late), irregular menstrual cycle, presence of PCO on USG and clinical signs of hyperandrogenism such as early acne or hirsutism, persistent severe acne, frequent relapse in acne, acne in facial 'V' area, persistent acne and hirsutism for more than two years.^{7,8}

Diagnosis of PCOS in Adolescents

Standardizing diagnostic criteria for PCOS during adolescence remains challenging, as frequently encountered manifestations of PCOS mimic normal pubertal physiological changes. These include irregular menstrual cycles, cystic acne, hirsutism and ultrasound appearance of polycystic ovaries. The prevalence of irregular cycles is approximately 85% due to the immature hypothalamic-pituitary-ovarian axis during the first year and reduces to 59% during the third year after menarche with stabilisation of the hormonal balance.⁹ Therefore, precautions should be taken to follow patients with irregular menstruation i.e cycles ≤ 20 days or ≥ 45 days longitudinally for 2 years post menarche/or ≥ 90 days even during the first year before making the diagnosis of PCOS to avoid over diagnosis^{10,11}.

Suggested criteria for the diagnosis of PCOS in adolescence.⁵

Required	Optional ^a	Not recommended ^b	Comments
1. Irregular menses / oligomenorrhea 2. Evidence of hyperandrogenism: a. Biochemical b. Clinical (e.g., progressive hirsutism)	1. PCOM 2. Severe cystic acne	1. Obesity 2. Insulin resistance 3. Hyperinsulinemia 4. Biomarkers (e.g., AMH, T/DHT ratio) 5. Acanthosis nigricans	1. Must generally be 2 years post-menarche 2. Must rule out other disorders of hyperandrogenism (e.g., NC-CAH, Cushing syndrome)

PCOS; polycystic ovary syndrome; PCOM, polycystic ovarian morphology; AMH, anti-Müllerian hormone; T/DHT, testosterone to dihydrotestosterone; NC-CAH, non-classical congenital adrenal hyperplasia, ^aThese criteria are often used in concert with the required criteria, but should not be used independently as diagnostic features. ^bThese criteria have been associated with PCOS but are not diagnostic.

Evidence based criteria used for the diagnosis of adolescent PCOS as recommended by the International paediatric and adolescent specialty societies are as follows¹²:

1. Clinical Features of PCOS

- Persistent menstrual disturbances (oligomenorrhea and secondary amenorrhea) beyond 2 years after menarche or primary amenorrhea in girls with completed puberty may suggest androgen excess (Level B).
- Mild hirsutism may be a sign of androgen excess when associated with menstrual irregularities (Level C).
- Moderate to severe hirsutism constitutes clinical evidence of androgen excess (Level B).
- Moderate or severe inflammatory acne unresponsive to topical therapy may require investigation of androgen excess (Level C).
- Isolated acne and/or alopecia should not be considered diagnostic criteria for PCOS in adolescence (Level C).
- Biochemical hyperandrogenism should be defined based on the methodology used, as no clear cut off for testosterone concentrations exists for adolescents (Level A).
- Biochemical evidence of hyperandrogenism based on elevations of total and/or free testosterone measured in a reliable reference laboratory documents hyperandrogenemia in a symptomatic adolescent (Level B).

2. Polycystic Ovarian Morphology

- The presence of polycystic ovarian morphology (PCOM) in an adolescent who does not have hyperandrogenism/oligo-anovulation does not indicate a diagnosis of PCOS (Level A).
- The measurement of ovarian volume, follicle number and size, and uterine dimensions may be useful in the evaluation of amenorrhea, but is not needed for PCOS diagnosis in adolescents (Level A).
- Abdominal ultrasound in adolescents, particularly obese girls, may yield inadequate information (Level C).

3. Biomarkers of PCOS

- AMH levels relate with the number of small antral follicles (2-5 mm) in the ovaries. Elevated AMH levels have been associated with PCOS. However, in adolescents, AMH should not be used as a criterion of PCOS may be due to the presence of higher AMH serum levels in healthy adolescents compared to adult women, with a wide normal range [13,14,15,16]. The use of AMH, T/DHT ratios, and specific proteins or microRNA as biomarkers of PCOS has not been validated in adolescents (Level C.).

4. Insulin Resistance

- IR, compensatory hyperinsulinemia, or obesity should not be considered as diagnostic criteria for PCOS in adolescents (Level A)

Management of Adolescent PCOS

Expert group recommendations for evidence based management of adolescent PCOS formulated by the Androgen Excess-PCOS Society and International paediatric and adolescent specialty societies are as follows⁵:

Baseline Treatments

1. Lifestyle Intervention

- Lifestyle intervention should be based on the combination of calorie-restricted diets, behavioural treatment, and exercise (Level A).
- Combined weight loss and physical exercise are the first-line therapy in overweight and obese girls (Level C). They decrease androgen levels, normalize menstrual cycles (Level A), and improve markers of cardio-metabolic health (Level B).
- Extremely obese adolescents respond poorly to lifestyle intervention (Level B).
- In normal-weight girls, increasing physical activity is effective in reducing the development of metabolic syndrome (Level C). However, the benefits of exclusive weight loss in these adolescents are not supported by RCTs (Level C).

2. Local Therapies/Cosmetic

- Photoepilation is the first-line management of localized hirsutism in PCOS (Level B). Diode and alexandrite lasers are preferred (Level C). The alexandrite laser is superior to IPL methods in facial hirsutism (Level B).
- Topical eflornithine is recommended as an adjuvant to photoepilation in girls with laser-resistant facial hirsutism aged 16 years or older, or as monotherapy in those where photoepilation is not indicated (Level A).
- The use of topical finasteride is not recommended based on existing data (Level C).

Pharmacotherapy

1. Metformin

- Metformin has beneficial effects in overweight or obese adolescents with PCOS, but only short-term data are available (Level A).
- In non-obese adolescents with PCOS and hyperinsulinemia, metformin improves ovulation and testosterone levels (Level B).

2. Anti-Androgens

- Anti-androgens reduce androgen excess features more than metformin in monotherapy (Level

B). Spironolactone is the most commonly used although data on efficacy compared to flutamide are limited (Level C).

- Anti-androgens should only be used when contraceptive measures are guaranteed.

3. Oral Contraceptive Pills

- There are no high-quality RCTs of specific OCP formulations for adolescents with PCOS to help decision-making in this population, and no specific

formulation can be recommended over another (Level B).

4. Combination Treatments

- Where available, triple low-dose combinations of insulin-sensitizing and anti-androgenic generics normalize cardiovascular risk and body composition more than combinations of only metformin and an anti-androgen and result in a more favourable post-treatment pattern of circulating androgens and ovulation rates than OCP intake (Level A).

Summary of medications used in the treatment of polycystic ovary syndrome in adolescent girls.⁵

Medication	Mechanism (s) of action	Dosage	Side effects	Contraindication
Estro-progestagen OCP	Inhibition of ovarian androgen secretion and increase in hepatic SHBG production, resulting in less circulating free androgens	21 out of 28 days/month	Breast tenderness, headache, increased risk of venous thromboembolism, tend to increase insulin resistance	Pregnancy, uncontrolled hypertension, liver dysfunction, complicated valvular heart disease, migraines with aura of focal neurologic symptoms, thromboembolism, diabetes complications, organ transplantation
Metformin	Upregulation of the energy sensors STK11 and AMPK Improvement of insulin sensitivity in muscle and adipose tissue Downregulation of hepatic gluconeogenesis (improves fasting blood glucose) Increase of GLP-1 secretion and GLP-1 receptor expression (improves postprandial blood glucose) Decrease of ovarian and adrenal androgen production	850 mg/day up to 1 g b.i.d	Gastrointestinal discomfort ¹ , lactic acidosis ²	Renal and liver dysfunction, surgery, use of contrast agents, heart failure, alcoholism, metabolic acidosis, dehydration, hypoxemia
Pioglitazone	Peroxisome proliferator-activated receptor-γ activator At low dose, inhibition of CDK5- mediated phosphorylation of peroxisome proliferator-activated receptor-γ	7.5 mg/day up to 30 mg/day	Weight gain (higher doses), bladder cancer risk inconclusive results; studies include only male diabetic patients >40 years, risk with cumulative doses >28,000 mg	Pregnancy, liver dysfunction, bladder cancer
Flutamide	Androgen receptor blockade	62.5 mg/day up to 250 mg/day	Dose-dependent hepatotoxicity Absent at doses of 1 mg/kg/day Feminization of male fetuses	Pregnancy, renal and liver dysfunction
Spironolactone	Aldosterone antagonism Androgen receptor blockade	50-200 mg/day	Mostly dose-dependent: irregular menstrual bleeding, headache, hypotension, nausea, decreased libido, feminization of male fetuses	Pregnancy, renal failure, hyperkalemia
Cyproterone acetate	Competition with dihydrotestosterone at receptor level Inhibition of 5α-reductase, prevents conversion of testosterone to dihydrotestosterone	50-100 mg/day Combined with OCP 2 mg/day	Liver toxicity, irregular menstrual bleeding, nausea, decreased libido, feminization of male fetuses	Pregnancy, renal and liver dysfunction
Finasteride	Inhibition of 5α-reductase, prevents conversion of testosterone to dihydrotestosterone	1-5 mg/day	Feminization of male fetuses, liver dysfunction (rare)	Pregnancy

OCP; oral contraceptive pill; SHBG, sex hormone-binding globulin; STK11, serine/threonine protein kinase; AMPK adenosine monophosphate activated protein kinase; b.i.d., bis in die. ¹Gradually increasing minimizes the appearance of gastrointestinal symptoms. ²Older patients with type 2 diabetes and renal failure.

Conclusion

Longitudinal prospective research studies need to be conducted for understanding the natural history of adolescents with PCOS or those who are at risk for developing PCOS in future. Studies should be designed to compare long term interventions using high-quality RCTs. Through such research studies, it is hoped that validated diagnostic criteria supported by robust clinical and hormonal findings can be established to so that timely diagnosis can be made while avoiding over diagnosis and unnecessary treatment in otherwise healthy normal pubertal girls. Comprehensive management requires a patient-specific, one to one approach for providing thorough education and counseling. Improvement in health of the adolescents with PCOS could improve pregnancy outcome and prevent disease in the next generation. Timely diagnosis of PCOS and adoption of healthy lifestyle modifications in symptomatic adolescent girls can prevent metabolic complications in future.

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Management of Infertile Women with PCOS



Dr Surveen G Sindhu

Surveen Ghumman Sindhu

Director & Head, Department of IVF & Reproductive Medicine, MAX Multispeciality Hospitals, Panchsheel, Saket, Patparganj & Vaishali

Incidence of polycystic ovary syndrome (PCOS) is 4-12% although many more women have polycystic morphology. PCOS has been the subject of intensive research in the last few years resulting in introduction of many new drugs which give therapeutic benefits to the metabolic and endocrinal impact of PCOS.

Women with PCOS may develop insulin resistance (IR) which is a reduced glucose response to a given amount of insulin and usually results from faults within the insulin receptor and post-receptor signaling. Annual rate of developing IR was 4.5% compared with 0.9% in the control population.¹ Many new insulin sensitizers have been tried and modification and new regimes for older ones have come in.

Metformin Therapy for PCOS - Current evidence

Metformin helps to reduce insulin resistance by inhibiting the production of hepatic glucose, decreasing lipid synthesis, increasing fatty acid oxidation and inhibiting gluconeogenesis. It enhances insulin sensitivity at the cellular level and also appears to have direct effects within the ovary. It was assumed that metformin would help to improve the reproductive outcome in insulin resistant women.

Earlier smaller studies had shown a significant benefit in terms of biochemical and clinical improvement with metformin, but recent RCT have conflicting reports. A recent Cochrane Review on 3848 women and 40 studies, stated no consensus on the dose and duration of metformin therapy.²

Role of Metformin in Weight Reduction - Current evidence

Metformin through its action on insulin was thought to help in weight reduction. Recent RCT do not conclude that metformin helps to reduce weight in any significant manner in comparison to placebo (3.98% vs 4.41%). Thus lifestyle changes still remain the mainstay for weight loss in PCOS.^{2,3}

Role of Metformin in Ovulation Induction- Current evidence

Since metformin improves insulin resistance, it also

has an impact on the hormonal profile and may help in ovulation induction in infertile PCOS.

I. Placebo and metformin

Metformin showed a slight benefit which was statistically significant in terms of live birth rate compared to placebo.²

II. Metformin vs clomiphene - Which should be taken as first line treatment?

A limited number of studies have compared metformin with clomiphene citrate. Legro et al in an RCT for three groups - Metformin alone Clomiphene citrate (CC) alone and metformin CC combined showed an live birth rates were 7.2% (15/208), 22.5% (47/209) and 26.8% (56/209), respectively. ⁴Similar pattern was observed for ovulation and pregnancy and it was concluded that CC remains first line treatment for ovulation induction and cannot be replaced by metformin.

III. Combining Metformin with clomiphene citrate (CC) for ovulation induction

It was shown that there were no significant differences in rates of ovulation (64% versus 72%), continuing pregnancy (40% versus 46%) or live birth rate (19% versus 27%) on addition of metformin to CC in all patients to improve reproductive outcomes. However, there were 2 subgroups identified which would benefit from addition of metformin - women with a BMI greater than 35 kg/m² and of those with CC resistance (OR 4.89). There was no benefit seen in terms of live birth rate.^{5,6}

Recent metanalysis comparing metformin to clomiphene in women with a BMI under 32 kg/m² reported no difference in terms of ovulation, pregnancy, live birth, miscarriage and multiple pregnancy rates with addition of metformin. A higher ovulation and pregnancy rate was seen as per a recent Cochrane review (2017) when combined therapy of clomiphene with metformin was given compared with clomiphene alone. There was no evidence that combined therapy improved the overall live births compared with clomiphene alone.²

IV. Combining Metformin with gonadotropins

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). There was no difference in miscarriage or multiple pregnancy rate or in incidence of OHSS.⁷

V. Metformin and In vitro fertilization

Stimulation response & Oocyte and embryo quality: It has been suggested that addition of metformin may improve the response to stimulation but there is no substantial study to conclude its effect on oocyte or embryo quality and egg yield.

Clinical Pregnancy Rate: A Cochrane review including 816 women and nine studies showed that clinical pregnancy rates were improved in the metformin group (OR 1.52).⁸ There was no effect on the miscarriage rate.

Ovarian Hyperstimulation syndrome: Those women using agonist cycle were benefited in terms of decrease of incidence of ovarian hyperstimulation (OHSS), however its role in the short GnRH antagonist protocol is uncertain.⁸

Metformin and Pregnancy

Metformin has not shown to be teratogenic and has shown a non significant reduction in miscarriage rate and preterm births. However its impact on pregnancy complications like gestational diabetes, pregnancy-induced hypertension, pre-eclampsia and neonatal morbidity is still being studied.⁹

Problems with use of metformin

1. The discontinuation rate is high with metformin due to severe gastrointestinal side effects. (16% vs 5% in CC).⁵
2. Optimal dose and duration for metformin for this purpose has still not been identified and adjustments for body weight and other factors are not done

Currently, the only acceptable indication for metformin is impaired glycemic control and documented insulin resistance and those with IGT or type II diabetes. 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. Long term use of metformin to improve metabolic parameters still remains controversial and lifestyle changes remain the mainstay of treatment in women of reproductive age.

Other Insulin-Sensitising Drugs

There is insufficient evidence to recommend the use of other insulin sensitisers, such as thiazolidinediones (glitazones), d-chiro-inositol and myo-inositol, in the treatment of anovulatory PCOS.

Thiazolidones

A large study has shown a dose-dependent increase

in ovulation rate with risk of liver toxicity with thiazolidones.¹⁰ Smaller studies using rosiglitazone therapy in obese and non-obese women demonstrated restored regular ovulatory cycles.¹¹ A systematic review and meta-analysis suggests that pioglitazone was more suitable for treating hyperinsulinemia and insulin resistance among PCOS patients, while metformin was more effective in reducing body weight. Well designed RCTs are needed to provide better evidence.¹²

Glucagon-like peptide 1 analogues (GLP-1 agonist) - Incretins (exenatide and liraglutide) in PCOS

Newer insulin-sensitising agents, such as glucagon-like peptide 1 (GLP-1) analogues (e.g. exenatide and liraglutide), are currently under investigation. Incretin is a natural hormone and causes release of insulin after meals. Exenatide and liraglutide are called incretin mimetics. Glucagon-like peptides receptor agonists are currently approved as anti-obesity agents. In a limited number of the women with PCOS, BMI and serum testosterone are the only variables that significantly decrease after 3 months of treatment with GLP-1 receptor agonists.¹³

Liraglutide Combined with Metformin

A study showed monotherapy with higher dose of 3 mg liraglutide was superior to liraglutide 1.2 mg in combination with metformin for weight reduction in PCOS. However, combination of two drugs further improved androgen profile beyond weight reduction and was associated with better tolerability.¹⁴

Inositols - Myo-inositol and d-chiro-inositol

In recent years, the introduction of inositols treatment with two inositol isomers, myo-inositol and d-chiro-inositol, has improved the endocrine and metabolic dysfunction, reduced weight, decreased androgen levels and regulated the menstrual cycle in PCOS. Inositols also have the potential to restore spontaneous ovulation and improve fertility in women with PCOS.¹⁵

Myo inositol vs Metformin

Myoinositol is being used for insulin resistance. Studies have shown that in comparison with metformin both treatments improved the glyco-insulinaemic features of obese PCOS patients, but only metformin seems to exert a beneficial effect on the endocrine and clinical features of the syndrome like weight menstrual regularity, hirsutism and LH, androgen and AMH levels.¹⁶

In a study by Nehra it was concluded that metformin did very well in all aspects, so it can be used as first line therapy in PCOS. Myo-inositol, however can be a new addition in the armamentarium for the treatment of PCOS with comparable efficacy.¹⁷

Myoinositol and Impact on embryo quality in IVF – Recent Evidence

Many PCOS patients have poor quality oocytes. A very recent trial in 2018 showed that myoinositol administration improved response by shortening duration and dose for stimulation, increased number of MII oocytes retrieved, showed increased quality of oocyte with better fertilization rates and more grade I embryos. The achieved pregnancy rates are at least in an equivalent or even superior to those reported using metformin as an insulin sensitizer with no moderate to severe side effects at a dosage of 4000 mg per day.¹⁸

However, a metaanalysis in 2017 of eight RCTs contradicted the above and showed myoinositol supplementation was insufficient to improve oocyte quality, embryo quality, or pregnancy rate. Future studies of appropriate dose, size and duration of inositol are vital to clarify its role in the management of PCOS.¹⁹

Combined Therapy Myo-inositol (MI) plus D-chiro-inositol(DCI)

Myo-inositol has been more beneficial in improving the metabolic profile, whereas d-chiro-inositol reduces hyperandrogenism better than myo-inositol.²⁰ Their physiological plasma ratio of MI/DCI is 40:1 and it has been shown that administration, in the physiological plasma ratio (i.e., 40:1) ensures better clinical results, such as the reduction of insulin resistance, androgens blood levels, cardiovascular risk and regularization of menstrual cycle with spontaneous ovulation.²¹

Impact on IVF results

D-chiro-inositol alone, mostly when given at a high dosage, exerts an unfavorable effect on oocyte quality. A correlation between myo-inositol/D-chiro-inositol ratio in follicular fluid and blastocyst quality was found with the ratio being significantly higher in the specimens rated as good quality blastocysts. Moreover, the pre-treatment with myo-inositol in women undergoing in vitro fertilization (IVF) may improve oocyte quality and ART outcome, compared to those rated as poor-quality blastocysts.²² Combined therapy rather than monotherapy with dichiroinositol was able to improve oocyte and embryo quality, as well as pregnancy rates, in PCOS women undergoing IVF-ET.²³

Inositols and alpha-lipoic and monacolin K

There is a proposed new natural link between inositols, with alpha-lipoic and monacolin K, a natural statin which reduces cholesterol, androgens, and lipoic acid by a mechanism affecting steroidogenesis²⁴

Acarbose

Acarbose belongs to a class of drugs called alpha-glucosidase inhibitors. It works by slowing the action of certain enzymes that break food down into sugars. This slows down digestion of carbohydrates to keep blood sugar from rising very high after eating.

A recent meta analysis showed that acarbose can reduce testosterone, TG, and VLDL, and increase HDL. Acarbose caused a significantly higher incidence of gastrointestinal disturbance.²⁵

Acarbose vs metformin in PCOS

Comparable high rates of regular menstrual cycles as well as ovulation could be achieved in both acarbose and metformin. No significant differences in metabolic and/or hormonal parameters could be detected. Regarding side effects, the rate of flatulence and/or diarrhoea was significantly lower for acarbose compared to metformin (38% vs. 80%).²⁶

Quercetin

There is an association between PCOS and obesity with low adiponectin levels which may be associated with insulin resistance. Quercetin is a flavonoid which increases the levels of adiponectin by 5.56% and is found to influence adiponectin-mediated insulin sensitivity in women with PCOS.²⁷

Vitamin D and PCOS

The vitamin D receptor and vitamin D metabolizing enzymes are found in reproductive tissues of women and men.²⁸ Vitamin D might influence steroidogenesis of sex hormones (estradiol and progesterone) in healthy women. Hypovitaminosis D is common in women with PCOS, seen more in women with androgen excess.²⁹ Vitamin D supplementation increased insulin sensitivity and decreased androgen levels in vitamin-D-deficient women with PCOS but did not have any effect in vitamin-D-deficient non-PCOS women. These results may indicate the possible role of vitamin D in the complex pathogenesis of PCOS.³⁰

Impact of Vitamin D on ovarian stimulation

Metformin treatment combined with calcium and vitamin D supplementation resulted in a higher number of dominant follicles when compared with metformin alone and placebo, which might indicate a beneficial effect on fertility.³¹ Another meta-analysis including 9 studies found that vitamin D significantly improved follicular development in PCOS women.³² On the basis of the link between vitamin D, granulosa cell luteinization and improved endometrial environment, it has been speculated that vitamin D supplementation may also improve ovulatory dysfunction and thereby fertility in PCOS patients.³³ Vitamin D supplementation significantly decreased AMH in PCOS women.³⁴

Vitamin D & Impact on endometrium

In a study by Asadi on outcome of IUI with Vitamin D supplementation, it was seen that while there was no treatment effect on pregnancy outcomes, the endometrial thickness was significantly higher with vitamin D supplementation when compared to the placebo group.³⁵

Association of vitamin D status with outcome parameters of fertility treatment

In a study it was observed that with CC there was a 44% reduced likelihood for live birth if 25(OH) D concentrations were < 75nmol/L. Progressive improvement in the odds for live birth was found at thresholds of ≥ 95 , ≥ 100 and ≥ 112.5 nmol/L, showing that Vitamin D status was also an independent predictor of live birth and ovulation after ovulation induction.³⁶

A systemic review by Trummer et al concluded that recent interventional trials investigating the effects of vitamin D supplementation in PCOS have yielded inconsistent results. This may be, at least in part, explained by the differences in study population sizes, study design (e.g. study durations of 8 weeks vs 12 weeks vs 6 months) or by different dosing regimens.³³

Statins

A recent Cochrane review stated that although statins improve lipid profiles and reduce testosterone levels in women with PCOS, there is no evidence that statins improve resumption of menstrual regularity or spontaneous ovulation, nor is there any improvement of hirsutism or acne.³⁷

Weight Reduction in Infertile PCOS women

I. Orlistat

Out of the anti-obesity drugs orlistat, sibutramine, and rimonabant the last two are withdrawn because of their side effects. Orlistat has shown significant weight loss and improved metabolic and cardiovascular indices. Orlistat use in obese PCOS patients leads to an improvement in insulin resistance, hyperandrogenemia, and cardiovascular risk factors.³⁸

II. Bariatric surgery

Bariatric surgery effectively attenuates PCOS and its clinical symptomatology including hirsutism and menstrual irregularity in severely obese women.³⁹ Bariatric surgery improves key diagnostic features seen in women with PCOS.⁴⁰ However, further research is required to identify whether weight loss surgery results in significant improvement in fertility of women with PCOS and to investigate which operation has the best results.⁴¹ Counseling is needed for perioperative pregnancy interval and care in pregnancy.

Non pharmacological Treatment and Herbal supplements

Berberine (BBR), Acupuncture, Vinegar, Resveratrol has shown positive effects improving hormonal and metabolic profile.⁴² A meta analysis on nutritional supplements and herbal medicines like Omega 3 fatty acid, Calcium, Selenium, Chromium, Inositol, Vitamin B complex, Cinnamon, Mentha, Camellia sinensis, *Cimicifuga racemosa* showed that they had no effect on improving symptoms of PCOS.⁴³

Ovulation Induction in PCOS

The problem with ovulation induction in PCOS are multiple. The LH levels may be high and thus interfere with stimulation by leading to a premature LH surge, poor pregnancy rate and high miscarriage rate. There may be hyperinsulinemia leading to increased androgen production resulting in disturbed folliculogenesis and poor response. Multiple antral follicles may respond to stimulation leading to ovarian hyperstimulation. There is a thin line between drug dose for optimal stimulation and hyperstimulation.

Clomiphene

CC has been the first drug of choice for ovulation induction in these cases. However, problems of a thin endometrium may require change of this drug. PCOS women may hyperstimulate with usual dose and may require just 25 mg daily for 5 days. With 50mg/day 46-52 % patients ovulate, with 100 mg/day 21-22 % ovulate and with 150 mg/day 8-12%.⁴⁴

Letrozole

Letrozole vs CC

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.⁴⁵ Letrozole is at least as effective, if not better than clomiphene in this group of women.

Dose and protocol of letrozole

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.⁴⁶ 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

Tamoxifen

Tamoxifen is also a SERM with an 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.

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.⁴⁷

Clomiphene resistant PCOS - Which drug and dose?

Increasing Clomiphene dose -Increase next cycle vs stair step protocol in same cycle

Conventional increase of the dose of clomiphene is done in the next cycle in CC resistant cases. However, it is seen that if higher doses of clomiphene were given 7 days after the last dose in the same cycle where no response occurs, the time to ovulation was decreased compared with the traditional protocol group (23.1±0.9 days vs 47.5±6.3 days). Ovulation rates were increased in the stair-step group compared with the traditional group at 150 mg (37%vs12%), and at 200 mg (21% vs 5%). Pregnancy rates were similar between groups once ovulation was achieved (18.1% vs 16.3%). The stair-step protocol had an increased incidence of mild side effects (vasomotor flushes, headaches, gastrointestinal disturbance, mastalgia, changes in mood) (41% vs 12%), but there was no difference in the incidence of severe side effects (headaches, visual disturbances).⁴⁸

Letrozole

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

- i. Letrozole: In clomiphene resistant PCOS, when compared with placebo, letrozole was shown to have 33.3 % ovulation rate compared with nil in the placebo group.⁴⁹
- ii. Letrozole vs higher dose of clomiphene: 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.⁵⁰ Letrozole is preferred to using a higher dose of CC in CC resistance.

iii. Letrozole vs Gonadotropin cycle in CC resistant cases: 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 when compared with HMG, 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 gonadotropins⁵¹

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.⁵²

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

Which Adjuvants are useful with clomiphene in CC resistant cases?

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)⁵³

Dexamethasone: 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).⁵³ It is usually given from day 5 to day 14. Dexamethasone is the only effective adjuvant

Laparoscopic Ovarian Drilling (LOD)

There was no clear evidence that LOD improves menstrual regularity or the androgenic symptoms of PCOS, better than most of the medical treatments used in the included studies. LOD was associated with fewer gastrointestinal side effects compared to metformin and clomiphene. The reduction in multiple pregnancy rates in women undergoing LOD makes this option attractive. However, there are ongoing concerns about the long-term effects of LOD on ovarian function.⁵⁴ A recent meta analysis in 2017 stated that LOD seems to markedly reduce circulating AMH, it remains uncertain

whether this reflects a real damage to ovarian reserve or normalisation of the high pre-operative serum AMH levels. Further long-term studies on ovarian reserve after LOD are required to address this uncertainty.⁵⁵

Unilateral vs bilateral Ovarian Drilling

Eight eligible trials (484 women) were analyzed. No significant difference was found in rates of ovulation, clinical pregnancy, live birth, or miscarriage when unilateral was compared with bilateral ovarian drilling. The reduction in AMH was comparable between the two procedures. A significantly higher AFC at 6-month follow-up was found with dose-adjusted unilateral drilling.⁵⁶

Ultrasound-Guided Transvaginal Ovarian Needle Drilling

Transvaginal needle drilling is simple, safe, and less invasive than LOD, but its effect on ovarian reserve appears to be transient and diminishes at 6 months. Multicenter studies are warranted to confirm its efficacy as a second-line treatment in patients with CC-resistant PCOS.⁵⁷

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. Unilateral drilling is as effective as bilateral. Several studies suggest the use of new or modified therapies for the treatment of obesity and metabolic syndrome associated with PCOS. Recent clinical trials have focused on inositols, statins, vitamin D, and quercetin for the treatment of obese women with PCOS. Non-pharmacological therapies are also under study. Their use as a combination or stand-alone therapy in women with PCOS needs to be investigated in future studies

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Announcement for Election of AOGD President and Vice President (2020-21)

Elections

- Nominations are invited from eligible AOGD members for the posts of
- President and Vice President of AOGD for the 2020 - 2021
- The nomination should be Proposed by one AOGD life member and seconded by two AOGD life members.
- The last date of filling the nominations is 30th June 2018.

Eligibility criteria

1. President AOGD has to be a faculty of medical colleges / leading, multidisciplinary clinic hospital with Para-clinic and clinical departments (oncology, radiology, pathology etc.)
2. Experience of having been chairperson of sub-committee of AOGD / FOGSI or experience as Vice President / Secretary / Treasurer / Editor of AOGD.
3. Life member of AOGD having above 10 years of experience in specialty after post-graduation and holding post of professor / senior consultant for more than 7 years.
4. Experience of conducting conferences, seminars or workshops etc.
5. In case of a tie after election, the senior most person out of the contestants will be nominated.

The application should be sent in writing to the AOGD Secretariat, Department of Obstetrics and Gynecology, Lady Hardinge Medical College & SSK Hospital New Delhi 110001 by 30th June 2018.

Diagnosis of Insulin Resistance in PCOS

Neeti Chhabra¹, Sonia Malik²

¹Consultant, Southend IVF, ²Programme Director and Head, Southend IVF, New Delhi



Dr Sonia Malik

Introduction

The ever growing pandemics of obesity and Type II Diabetes mellitus have highlighted the phenomena of Insulin resistance. This has lead to a widened research into the role of insulin in the various physiological processes, its synthesis, secretion and action from the molecular to whole body level. Insulin is a peptide hormone secreted by the beta cells of the pancreatic islets. It is responsible for maintaining the normal blood glucose levels by facilitating cellular glucose uptake, promoting carbohydrate, protein and fat metabolism. It has mitogenic effects thus participating in cell division and growth.

Insulin Resistance Syndrome

Insulin resistance is a condition in which insulin mediated glucose disposal fails to occur despite normal or elevated insulin levels. The onset of insulin resistance manifests as post prandial hyperinsulinemia followed by fasting hyperinsulinemia and finally hyperglycemia. When insulin resistance occurs in the peripheral tissues like the muscle and adipose, the pancreatic beta cells produce a compensatory hyperinsulinemia to maintain normal blood glucose levels. Such patients usually have a cluster of abnormalities and related outcomes referred to as the Insulin resistance syndrome. One of the most sensitive pathways of insulin action is prevention of lipolysis in the adipose tissue and inhibition of the action of lipoprotein lipase enzyme. Thus, when insulin resistance occurs, increased lipolysis produces more fatty acids which impair insulin mediated glucose uptake and accumulate as triglycerides in the cardiac and skeletal muscles. Increased glucose production and triglyceride accumulation are seen in the liver.

Metabolic syndrome is the clinical entity that identifies these patients at risk of cardiovascular morbidity and mortality. Insulin resistance is a major risk factor in the development of Type II Diabetes Mellitus, hypertension, dyslipidemia, atherosclerosis and stroke.

The insulin resistance syndrome encompasses the following-

- Glucose intolerance
- Dyslipidemia
- Endothelial dysfunction
- Elevated pro coagulant factors
- Elevated inflammatory markers
- Hemodynamic changes
- Abnormalities in uric acid metabolism

- Increased ovarian testosterone secretion
- Sleep disordered breathing

Insulin resistance is associated with the following disorders-

- Type II Diabetes Mellitus
- Polycystic ovarian syndrome
- Essential hypertension
- Cardiovascular disease
- Non alcoholic fatty liver disease
- Sleep apnoea

The following are the physical features associated with Insulin resistance syndrome-

- Acanthosis Nigricans
- Signs of hyperandrogenism - hirsutism, acne and oligomenorrhoea

Two types of insulin resistance syndromes have been described in adults-

- Type A -affects young women. Includes severe hyperinsulinemia, obesity and hyperandrogenism. They are associated with a defect in the insulin signaling pathway.
- Type B-affects middle aged women. Includes severe hyperinsulinemia, autoimmune disorders and hyperandrogenism. They have autoantibodies directed at the insulin receptor

Insulin Resistance Syndrome and Polycystic Ovarian Syndrome

PCOS is the most common metabolic abnormality encountered in young adults and women of reproductive age group. There is a strong relation between insulin resistance and PCOS. Patients who are genetically predisposed to develop insulin resistance due to defects in insulin signal transduction have a risk of developing PCOS with insulin resistance preceding the clinical manifestations of PCO. Insulin resistance is a common feature in obese and, to a lesser extent, in lean PCOS. Insulin sensitivity is decreased upto 35-40% in women with PCOS in comparison to normal women. Increased circulating insulin levels cause hyper androgenism in these women by stimulating increased ovarian androgen production, and by inhibiting hepatic SHBG production. Insulin and Luteinizing hormone act synergistically to cause hyper androgenism.

High local androgen concentrations contribute to the polycystic morphogenesis of the ovaries. They do so by conversion to more potent 5 α -reduced androgens. These

cannot be aromatized to estrogen. They also inhibit aromatase activity and FSH induction of LH receptors on granulosa cells. This impedes progressive follicular development. Thus, new follicular growth does occur but arrests before full maturation. This leads to multiple small cysts measuring 2-10 mm in diameter surrounded by hyperplastic theca cells. These atretic follicles contribute to an expanding ovarian stroma that increases in volume over time and starts a self propagating cycle of hyper androgenism and chronic anovulation.

Tests for Insulin Resistance

Our understanding of insulin resistance has improved over the years but still there are many caveats to the diagnosis of the same. Many methods and indices have been used to diagnose insulin resistance. Most of the methods employed are difficult to apply in clinical

Practice and clinical signs still are the best guide. Since compensatory hyperinsulinemia is highly correlated with Insulin Resistance, this is a better way to identify the same than do measurements of glucose intolerance. The analytic methods for insulin measurements are not standardized and it is thus difficult to compare values of plasma insulin concentrations between laboratories.

Out of all the methods employed, the Hyper insulinemic euglycemic clamp and intravenous Glucose Tolerance test are used as reference standards. There are other indices which can be divided into two groups-

- *Indices using plasma concentration of insulin, glucose and triglycerides-*
 - HOMA -IR
 - QUICK-I
 - Mc Auley
- *Indices using plasma concentration of insulin and glucose obtained during 120 mins of 75 gm glucose tolerance test*
 - Matsuda
 - Belfiore
 - Cederholm
 - Avignon
 - Stumvoll

Out of these, the HOMA -IR and QUICK -I are used for clinical purposes while the others are for epidemiological and research purposes.

The hyperinsulinemic euglycemic glucose clamp is the Gold standard method for quantifying insulin sensitivity. It is a direct measure of insulin under steady-state conditions. But it has the disadvantage of being laborious and involving intra venous infusion of insulin with frequent blood samples to be taken over a 3 hour period. It is expensive, experimentally demanding and complicated when large scale epidemiological studies are involved.

Thus, there was a need to establish surrogate markers for insulin resistance. They are as under-

Surrogate markers of Insulin resistance

- Oral glucose tolerance test with 75 gms glucose is used to detect glucose intolerance. It involves the administration of glucose to find out how rapidly it is cleared from the blood. It explains the efficiency of the body to utilize glucose after a glucose load. During OGTT, after 8 to 10 h of fasting, blood glucose levels are determined at 0, 30, 60, and 120 min following an oral glucose load of 75 gm. The test is easy. It helps in estimating other surrogate indices also. The disadvantage is that it is only helpful in diagnosing glucose tolerance but not insulin resistance.
- Fasting insulin is the most practical method to measure insulin resistance. It detects insulin resistance before the clinical disease appears. But it lacks standardisation of the insulin assay procedure involved.
- Glucose / insulin ratio (G/I ratio) has comparable insulin sensitivity to Glucose Tolerance Test. It is highly sensitive and specific for measuring insulin sensitivity but it does not reveal the physiology of the insulin sensitivity.
- The insulinogenic index (IGI) is an index of beta cell function. It measures the first phase insulin response to glucose challenge but is not validated test.
- The Homeostasis model assessment assess inherent beta cell function and insulin sensitivity. This test is simple, minimally invasive and it predicts the fasting steady state levels of insulin and glucose. This test too needs validation.
- The Quantitative insulin sensitivity check index (QUICKI) is a mathematical transformation of Fasting glucose and insulin. This test is precise, consistent and minimally invasive. Because of the variation in the assays of insulin used, the normal ranges need to be established.

Imminent markers of insulin resistance

With continued research into insulin resistance, its pathophysiology and diagnosis, certain inflammatory markers have gained importance. The following are the imminent markers of insulin resistance-

- Insulin growth factor binding protein-1 (IGFBP-1)
- sCD36 (solubleCD36)
- C-reactive protein (CRP)
- Ferritin
- Adiponectin
- Tumour necrosis factor (TNF alpha)
- Resistin
- C3 complement
- Glycosylated hemoglobin (Hb)A1c
- Protein kinase C (PKC) in microangiopathy
- Sex hormone-binding globulin (SHBG) in hyperandrogenic syndrome

Insulin growth factor binding protein-1

- It is a new potential plasma marker to assess insulin resistance.

- This has a good correlation with FSIVGTT assessment of insulin sensitivity, mainly in children younger than 10 years.

Soluble CD 36

- It is a proatherogenic molecule that scavenges oxidized low-density lipoprotein, leading to foam cell formation. Hyperglycemia and altered macrophage insulin signaling in insulin resistance leads to increased expression of CD36.
- The marker is also elevated in patients with type 2 diabetes and insulin resistance.

C-reactive protein

- CRP is an indicator of systemic subclinical inflammation.
- It has a prognostic value in predicting the future risk of cardiovascular events.
- CRP is associated with several surrogate measures of IR like fasting insulin, the McAuley index, HOMA, QUICKI, the Insulin: glucose ratio and the Avignon index in non-diabetics.
- It is easily available and simple to measure.

Ferritin

- Ferritin is an intracellular iron storage protein.
- Ferritin has been associated with both hyperinsulinemia and hypertriglyceridemia.
- Iron deposition in various tissues affects insulin sensitivity and function, thereby leading to insulin resistance and inflammation.
- Studies suggest a link between markers of insulin resistance (HOMA-IR, fasting insulin) and ferritin
- The plasma levels of ferritin positively correlate with fasting insulin and fasting glucose levels.

Adiponectin

- Adiponectin has pleiotropic insulin-sensitizing effects and hence is considered as a key molecule in the pathogenesis of metabolic syndrome
- It lowers hepatic glucose production and increases glucose uptake and fatty acid oxidation in skeletal muscle.
- Adiponectin levels are decreased in obesity and are inversely correlated to insulin-resistant states.
- There is a strong negative correlation with HOMA in individuals without the metabolic syndrome as compared to those with metabolic syndrome.

Tumour necrosis factor alpha

- TNF has been proven to have a relation to insulin resistance measured by HOMA-IR or insulin clamp and to metabolic syndrome status.

Resistin

Few studies demonstrate a relation between insulin

resistance as measured by HOMA -IR and resistin levels .

C3 complement

- The main activation fragment of C3, C3a desArg (acylation stimulating protein) favours glucose transmembrane transport and the synthesis of triglycerides in adipocytes. This suggests that it has insulin-like properties.
- C3 is linked with insulin resistance (as defined according to the homeostasis model assessment (HOMA), independent of the components of the metabolic syndrome.

Glycosylated hemoglobin

- HbA1c has been proposed as a surrogate marker for the assessment of metabolic syndrome, thereby estimating IR because of various factors.
- Upper normal levels of HbA1c in the range of 5.7%-6.4% have been found to have a relation with insulin resistance syndrome.

Sex hormone-binding globulin

- It is a marker of Insulin Resistance in obese women suffering from hyperandrogenic syndrome.

Protein kinase C in microangiopathy

- Implicated in the activation of the protein kinase C β isoform (PKC β) which is mediated by hyperglycemia.
- It acts as a potential surrogate marker for microangiopathic diseases, and diabetic retinopathy in particular.

Conclusion

Insulin resistance is an ever growing pandemic with multi pronged health ramifications including the PCO manifestations. Its diagnosis is laborious and involves multiple complicated and intricate tests. There is a need to extend the research and establish easily available, simple, inexpensive and precise methods for the diagnosis of the same which have greater application and acceptability. Till then it is imperative to rely on the clinical markers supported by the validated laboratory tests to diagnose the syndrome in PCO women.

Suggested Reading

1. Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A. Assessment of insulin sensitivity/resistance. *Indian Journal of Endocrinology and Metabolism*. 2015;19(1):160-164.
2. Singh B, Saxena A, Surrogate markers of insulin resistance: A review. *World J Diabetes*. 2010 May 15;1(2):36-47.
3. Wilcox G; Insulin and insulin resistance; *Clin Biochem Rev*. 2005 May;26(2):19-39.
4. Harrison's principles of Internal Medicine, 18th ed.
5. Chronic Anovulation and the Polycystic ovarian syndrome. *Clinical gynecologic endocrinology and infertility*, Leon Speroff, 8th ed. Philadelphia: Wolter Kluwer; 2011. p495-532.

CASE APPROACH

Patient with Hyperandrogenism

Ram Kumar Patidar¹, Venus Dalal², Alka Kriplani³

¹Junior Resident, ²Senior Resident, ³Professor & Head Department of Obstetrics and Gynaecology, AIIMS, New Delhi



Dr Alka Kriplani

Hyperandrogenism is characterized by excess production of androgens by the ovaries, adrenal glands or peripheral tissues. The most common clinical manifestation of hyperandrogenism in women is hirsutism. Although most causes of hyperandrogenism are benign, rapid onset or progressive worsening of symptoms suggests malignancy.

Evaluation of Hyperandrogenism

History

- Hirsutism-Age of onset, growth pattern(slow/rapid)
- Acne
- Infertility
- Excess hair fall (female pattern alopecia), Deepening of voice, Decrease in breast size
- Affected day-to-day life, anxiety, depression
- Other Symptoms-Weight gain, Cold intolerance, Headache, Visual disturbance, pain/lump abdomen, Galactorrhoea
- Menstrual history: Amenorrhea, delayed puberty, Infrequent cycles, decreased menstrual flow
- Family history- PCOS, metabolic syndrome, CAH, Idiopathic
- History of Drugs intake- Androgens, Danazol, 19-norprogesterone, Minoxidil

Physical Examination

Anthropometry	Ht, Wt, BMI, Waist hip ratio (obesity)
Hyperinsulinemia	Acanthosis nigricans
Hyperandrogenism	Acne, seborrhea, androgenic alopecia, hirsutism
Virilization	Frontotemporal balding, ↓breast size, deepening voice, Clitoral hypertrophy
Cushing disease	Striae, moon facies, fragile skin, proximal myopathy
Thyroid disease	Textural skin change, goitre, hair loss
Hyperprolactinemia	Galactorrhoea

Modified Ferriman-Gallwey score

Hair growth from 9 Androgen sensitive body areas: score 0-4 for each site

- | | | |
|-----------------|---------------|------------|
| • Upper lip | Chin | Chest |
| • Upper abdomen | Lower abdomen | Upper arm |
| • Thighs | Upper back | Lower back |

>8 Hirsutism
8-15: Mild
>15: Moderate to Severe

Investigations

Day 2/3 S. LH, S.FSH

Blood glucose, HbA1C, Fasting insulin

Causes of hyperandrogenism

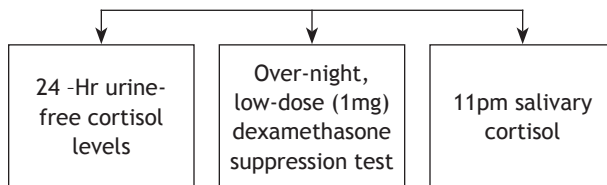
Diagnosis	Incidence	Signs & Symptoms	Lab test
PCOS	82%	Infrequent cycles, weight gain, infertility	Polycystic ovary on USG, raised fasting insulin, reversal of LH/FSH ratio
HAIR-AN syndrome	3%	Acanthosis nigricans	↑ Fasting BS and insulin levels
Idiopathic hirsutism	5%	Regular menses	Normal androgen levels
Idiopathic hyperandrogenism	7%	Regular menses	↑ Androgen levels
CAH	1%	Virilization, frontotemporal balding, deepening of voice, clitoromegaly	Elevated ↑ 17-OHP
Androgen secreting neoplasm(<1%)	Ovarian tumor	Sertoli-Leydig cell, theca cell, Hilus cell tumor	↑ Testosterone & Normal DHEAS
	Adrenal tumor	Adrenal adenoma/Carcinoma	Normal/↑ Testosterone & ↑ DHEAS
Other causes	Hypothyroidism, Hyperprolactinemia, Cushing syndrome		

S.TSH, S.PRL

Lipid profile

Special Laboratory investigations

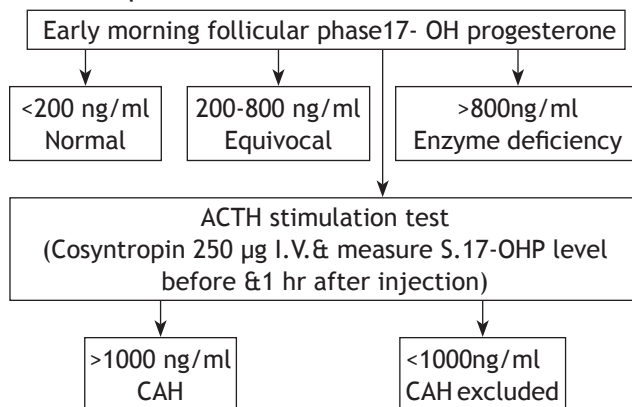
- Testosterone:
Free Androgen Index = $S. \text{ total Testosterone} / \text{SHBG} \times 100$
- Dehydroepiandrosterone sulphate(DHEAS)
Elevated S. testosterone & Normal DHEAS-ovarian source most likely
Elevated DHEAS level & Normal/ \uparrow S. testosterone-adrenal source most likely
- Cortisol levels
If Cushing's syndrome suspected



*A -ve initial test excludes Cushing's syndrome, 2 different tests should be +ve to confirm diagnosis

- 17-hydroxyprogesterone: Elevation of the 17-OHP level, an intermediate in the synthesis of adrenocortical hormones, is the distinguishing characteristic of 21-hydroxylase (CYP21) deficiency, the most common form of CAH.

CAH is suspected



Radiological Investigations

- USG pelvis: To look for polycystic ovarian morphology, ovarian tumor, adrenal tumor
- MRI Brain: Recommended when prolactin levels $>100 \text{ ng/ml}$ to rule out pituitary adenoma
- Imaging of adrenal glands: CECT or MRI if neoplastic cause is suspected

Polycystic Ovary Syndrome

Most common cause of hyperandrogenism. According to NIH 1990 criteria, approximately 70% of PCOS patients have elevated serum levels of free testosterone.

HAIR-AN Syndrome

The HAIRAN syndrome is an acronym for a disorder in women that consists of hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN).

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) most common cause is 21-hydroxylase deficiency. This enzyme defect leads to the accumulation of steroid precursors, which are subsequently converted to androgen. Classic CAH presents at birth with virilization of the female external genitalia, whereas late-onset (non classic) CAH is milder and typically does not present until early puberty.

Androgen-Secreting Tumors

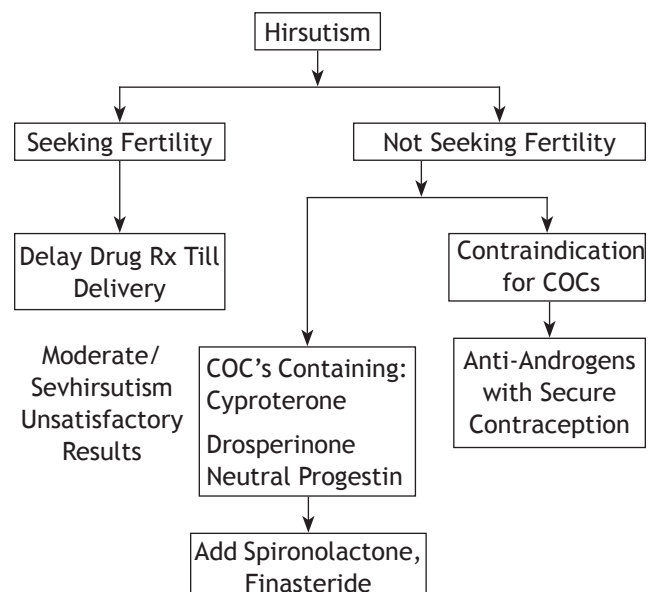
Although androgen-secreting tumors are rare ($<1\%$ of patients), they must be excluded in women who develop hirsutism or signs of virilization, including increased muscle mass, breast atrophy, clitoromegaly, and deepening of the voice, over a short period of time.

Management

The management of hyperandrogenemia in women generally focuses on treating the clinical consequences of the underlying disorder (hirsutism, anovulatory bleeding or resulting infertility). One key fact regarding the treatment of androgen excess is that patients generally require combination therapy, combining not just medications but approaches.

Hirsutism

A combination of psychological counselling, weight loss, pharmacological therapies and mechanical hair removal is recommended for the management of patients with hirsutism.



- Combined Oral contraceptives: 1st line of treatment
Cyproterone acetate containing: EE 35mcg+ CPA 2mg
Drospirenone containing: EE 30mcg/20mcg + Drospirenone 3mg
- Antiandrogen:
 - Spironolactone 50-100mg BD
 - Cyproterone acetate
 - Finasteride 5mg OD
- Insulin sensitizing agents: metformin, thiazolidinediones
- GnRH agonist : only when OCP's and antiandrogen fails
- Glucocorticoids: in case of CAH
- Topical treatment: eflornithine 13.9% cream, mostly used in postmenopausal female with hirsutism

Follow up: No significant reduction in hair growth may occur upto 6 months.

mFG scoring on follow up visits

Photographs of affected areas

Initiation of treatment should be based on the patient's perception of the problem, rather than quantitative assessment of hirsutism.

Acne:

COC's

Topical agents: Benzoyl peroxide, Adapalene, Isotretinoin, Retinoids

Oral/topical antibiotics

Female pattern hair loss:

The first-line treatment of female pattern hair loss is 2% topical minoxidil.

Infertility and long term complications:

Women with hirsutism and PCOS should also be informed about other problems related to the syndrome such as anovulatory infertility and long-term health

consequences including the risk of diabetes, and the potential risks of cardiovascular disease and endometrial cancer.

Ovulation induction: First-line SERM (clomiphene citrate)

*Combining these drugs with metformin or myo-inositol has shown to improve pregnancy rate

Second-line treatment-low dose gonadotropin therapy with best results but the risk of multiple pregnancies and ovarian hyperstimulation syndrome is increased

Treatment for Other Causes of Hyperandrogenism

CAH- Glucocorticoids (ie, dexamethasone, prednisolone)

Hyperprolactinemia-Cabergoline 0.25-0.5mg once/twice weekly

Bromocriptine start with 0.625-1.25mg daily, therapeutic dose 2.5-15mg /day

Conclusion

In patients presenting with signs and symptoms of hyperandrogenism, a careful history, including time of onset (gradual or rapid), examination and necessary blood investigation are critical. Rapid onset of hirsutism or virilization suggests an androgen-secreting tumor, whereas gradual onset of symptoms at puberty suggests PCOS, the most common underlying cause of hirsutism. Oral contraceptives are the most widely used drugs for suppressing ovarian androgen production in women with hirsutism; however, more specific therapy is warranted in some diseases.

Suggested Reading

1. Escobar-Morreale HF. Diagnosis and management of hirsutism. *Ann N Y Acad Sci.* 2010 Sep;1205:166-74.
2. AACE Medical Guidelines For Clinical Practice For The Diagnosis And Treatment Of Hyperandrogenic Disorders *Endocr Pract.* 2001;7(No. 2).

Forthcoming Events

- CME on "Evidence Based Management of High Risk Pregnancy" under the aegis of AOGD Fetal Medicine Sub-committee 13th May 2018 organized by Division of Fetal Medicine, Department Obs & Gynae, AIIMS, New Delhi
- CME on "Molecular Pathology of Gynecologic Oncology" on 18th May 2018, 1:00pm onwards at Auditorium Indraprastha Apollo Hospital, Sarita Vihar.. Contact: Dr Sarika Gupta - 9313295008, Mrs. Rupinder Kaur - 9811913335
- CME on Pre-eclampsia: Current Update on 19th May 2018, 1:00 - 4:00pm. Contact: Dr Kiran Aggarwal - 09312277346, Dr Anuradha Singh- 09891387779
- Next AOGD Clinical Meeting on 25th May 2018, 4:00 - 5:00pm at BLK Super Speciality Hospital, New Delhi
- CME on Endometriosis organized by AOGD Endometriosis sub-committee on 10th June 2018, 1:00 - 5:00pm at India International Centre. Convener: Dr Renu Mishra
- 21st Practical Course and CME organized by Department of Obstetrics and Gynecology MAMC to be held at Maulana Azad Medical College Auditorium from 7th - 9th September 2018. For details contact Dr Deepti Goswami 9968604348 / Dr Sangeeta Bhasin 9873617591
- 40th AOGD Annual Conference on 24th & 25th November, 2018 at India Habitat Centre



Dr Ratna Biswas

Menopause: May 7, 2018 - Volume Publish Ahead of Print - Issue - p doi: 10.1097/GME.0000000000001116

Is Ovarian Reserve associated with Body Mass Index and Obesity in Reproductive Aged Women? A meta-analysis

Moslehi N, Shab-Bidar S, Ramezani Tehrani F, Mirmiran P, Azizi F

Objective

The associations of body mass index (BMI) and obesity with ovarian reserve are controversial. This systematic review and meta-analysis was conducted to investigate the associations in reproductive-aged women.

Methods

PubMed and Scopus were searched up to December, 2016. Original studies on the association of BMI with ovarian reserve markers, anti-Mullerian hormone (AMH), follicle-stimulating hormone (FSH), inhibin B, and antral follicle count (AFC), either according to BMI categories or a continuous variable, were selected. Analyses were stratified into three groups based on polycystic ovary syndrome (PCOS) and fertility status of women.

Results

Of 4,055 records identified, 45 studies were eligible for inclusion. Comparing the obese with nonobese, the pooled mean differences (MDs) and 95% confidence intervals (CIs) were -1.08 (95% CIs -1.52, -0.63) ng/mL

for AMH, -0.22 (95% CIs -0.39, -0.06) mIU/mL for FSH, -0.09 (95% CIs -0.60, 0.42) for AFC, and -21.06 (95% CIs -41.18, -0.85) pg/mL for inhibin B in overall populations. The MDs were significant for AMH in fertile non-PCOS and PCOS women, and for FSH only in PCOS women. Fisher's Z showed significant correlations of BMI with AMH in the overall populations (-0.15 [95% CIs -0.20, -0.11]) and in all subgroups, and with FSH in the fertile non-PCOS women (-0.16 [95% CIs -0.28, -0.04]).

Conclusion

Ovarian reserve markers of AMH and FSH are significantly lower in obese than in nonobese women, and BMI is negatively correlated with AMH in all study populations, and with FSH in fertile non-PCOS subgroups. PCOS and fertility status do not appear to affect the associations.

Editors Comment: Obesity plays a central role in the pathogenesis of PCOS and is responsible for majority of the clinical manifestations including infertility. Life style modifications and control of obesity is pivotal for management of PCOS.

Am J Obstet Gynecol. 2018 Apr 7. pii: S0002-9378(18)30279-5. doi: 10.1016/j.ajog.2018.04.002.

Long-term Mortality Risk and Life Expectancy following Recurrent Hypertensive Disease of Pregnancy

Theilen LH, Meeks H, Fraser A, Esplin MS, Smith KR, Varner MW

Background

Women with a history of hypertensive disease of pregnancy have increased risks for early mortality from multiple causes. The effect of recurrent hypertensive disease of pregnancy on mortality risk and life expectancy is unknown.

Objective

We sought to determine whether recurrent hypertensive disease of pregnancy is associated with increased mortality risks.

Study Design

In this retrospective cohort study, we used birth certificate data to determine the number of pregnancies affected by hypertensive disease of pregnancy for each woman delivering in Utah from 1939 through 2012. We

assigned women to 1 of 3 groups based on number of affected pregnancies: 0, 1, or ≥ 2 . Exposed women had ≥ 1 affected singleton pregnancy and lived in Utah for ≥ 1 year postpartum. Exposed women were matched 1:2 to unexposed women by age, year of childbirth, and parity. Underlying cause of death was determined from death certificates. Mortality risks by underlying cause of death were compared between exposed and unexposed women as a function of number of affected pregnancies. Cox regressions controlled for infant sex, gestational age, parental education, ethnicity, and marital status.

Results

We identified 57,384 women with ≥ 1 affected pregnancy (49,598 women with 1 affected pregnancy and 7786 women with ≥ 2 affected pregnancies). These women were matched to 114,768 unexposed women. As of 2016,

11,894 women were deceased: 4722 (8.2%) exposed and 7172 (6.3%) unexposed. Women with ≥ 2 affected pregnancies had increased mortality from all causes (adjusted hazard ratio, 2.04; 95% confidence interval, 1.76-2.36), diabetes (adjusted hazard ratio, 4.33; 95% confidence interval, 2.21-8.47), ischemic heart disease (adjusted hazard ratio, 3.30; 95% confidence interval, 2.02-5.40), and stroke (adjusted hazard ratio, 5.10; 95% confidence interval, 2.62-9.92). For women whose index pregnancy delivered from 1939 through 1959 ($n = 10,488$), those with ≥ 2 affected pregnancies had shorter additional life expectancies than mothers who had only 1 or 0 hypertensive pregnancies (48.92 vs 51.91 vs 55.48 years, respectively).

Conclusion

Hypertensive diseases of pregnancy are associated with excess risks for early all-cause mortality and some cause-specific mortality, and these risks increase further with recurrent disease.

Editors Comment: Hypertension in pregnancy is an indicator of future risk of hypertension and related complications. Hence women should be monitored for development of hypertension in later life and should control their blood pressure to avert morbidity and mortality.

Am J Obstet Gynecol. 2017 Dec;217(6):685.e1-685.e5. doi: 10.1016/j.ajog.2017.08.110. Epub 2017 Sep 6.

Aspirin for Evidence-Based Preeclampsia Prevention Trial: Influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia

Wright D, Poon LC, Rolnik DL, Syngelaki A, Delgado JL, Vojtassakova D, de Alvarado M, Kapeti E, Rehal A, Pazos A, Carbone IF, Dutemeyer V, Plasencia W, Papantoniou N, Nicolaides KH

The Aspirin for Evidence-Based Preeclampsia Prevention trial was a multicenter study in women with singleton pregnancies. Screening was carried out at 11-13 weeks' gestation with an algorithm that combines maternal factors and biomarkers (mean arterial pressure, uterine artery pulsatility index, and maternal serum pregnancy-associated plasma protein A and placental growth factor). Those with an estimated risk for preterm preeclampsia of >1 in 100 were invited to participate in a double-blind trial of aspirin (150 mg/d) vs placebo from 11-14 until 36 weeks' gestation. Preterm preeclampsia with delivery at <37 weeks' gestation, which was the primary outcome, occurred in 1.6% (13/798) participants in the aspirin group, as compared with 4.3% (35/822) in the placebo group (odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74).

Objective

We sought to examine the influence of compliance on the beneficial effect of aspirin in prevention of preterm preeclampsia in the Aspirin for Evidence-Based Preeclampsia Prevention trial.

Study Design

This was a secondary analysis of data from the trial. The proportion of prescribed tablets taken was used as an overall measure of compliance. Logistic regression analysis was used to estimate the effect of aspirin on the incidence of preterm preeclampsia according to compliance of $<90\%$ and $\geq 90\%$, after adjustment for the estimated risk of preterm preeclampsia at screening

and the participating center. The choice of cut-off of 90% was based on an exploratory analysis of the treatment effect. Logistic regression analysis was used to investigate predictors of compliance $\geq 90\%$ among maternal characteristics and medical history.

Results

Preterm preeclampsia occurred in 5/555 (0.9%) participants in the aspirin group with compliance $\geq 90\%$, in 8/243 (3.3%) of participants in the aspirin group with compliance $<90\%$, in 22/588 (3.7%) of participants in the placebo group with compliance $\geq 90\%$, and in 13/234 (5.6%) of participants in the placebo group with compliance $<90\%$. The odds ratio in the aspirin group for preterm preeclampsia was 0.24 (95% confidence interval, 0.09-0.65) for compliance $\geq 90\%$ and 0.59 (95% confidence interval, 0.23-1.53) for compliance $<90\%$. Compliance was positively associated with family history of preeclampsia and negatively associated with smoking, maternal age <25 years, Afro-Caribbean and South Asian racial origin, and history of preeclampsia in a previous pregnancy.

Conclusion

The beneficial effect of aspirin in the prevention of preterm preeclampsia appears to depend on compliance.

Editors Comment: Low dose aspirin is in the forefront as primary drug of choice for prevention of preeclampsia. It should be started early in pregnancy to have maximum beneficial effect. Compliance to dosage and schedule is mandatory for good outcome.

Clinical Proceedings of AOGD Clinical Meeting held at Indraprastha Apollo Hospital on 23rd April, 2018

An Interesting Case of Delayed Puberty

Ranjana Sharma¹, IPS Kochar², Ghazal Datta³

¹Senior Consultant, Department of OBS-GYN, ²Senior Consultant, Department of Paediatric Endocrinology, ³Registrar, Department of OBS-GYN, Indraprastha Apollo Hospitals, New Delhi

Case Summary

A 13years 7month-old girl presented in Gynaecology OPD with complaints of failure to attain periods, absent pubic hair and breast development, and weight gain since childhood. Her parents had consulted multiple gynaecologists in the past and were told that there was no hope of achieving menarche and puberty as their daughter had a small uterus and ovaries. She was referred to our hospital for further investigations and management. There was no history suggestive of thyroid derangements, chronic illnesses and medication in the past. She had no complaints of headache, loss of smell and vision problems.

She was born out of non-consanguineous marriage and was the eldest of the three siblings. Her antenatal and perinatal history was unremarkable. She was a student of the 7th standard with a good scholastic performance. Her mother attained menarche at the age of 14 years. There was no history of similar complaints in the family.

On examination, her weight was 58 kg and BMI of 30.9 kg/m². Her height was 137cm which was less than 5th centile for the age and sex, although her father's and mother's heights were 154 cm and 148 cm respectively and the mid parental height was 144.5 cm. Bilateral breasts were pre-pubertal (Tanner stage 1) with absent pubic or axillary hair. Rest of the systemic examination was within normal limits and the external genitalia looked normal.

She was co-managed with paediatric endocrinologist for her short stature with delayed puberty. The hormone profile revealed low FSH and LH (1.34 mIU/ml and 0.299 mIU/ml respectively) with an Estradiol of 20 pg/ml pointing towards hypogonadotropic hypogonadism. Thyroid function tests and prolactin were within normal limits. Considering her short stature, IGF-1 level was requested, and the values were low at 77.4 ng/ml (Normal range - 199- 496 ng/dl). Serum Cortisol was normal (15mcg/dl). A normal CBC and ESR ruled out any chronic disease. Screening for coeliac disease was negative. The MRI brain revealed no abnormality. Her LFT showed mildly raised SGOT/SGPT at 47 U/L and 61 U/L respectively, with grade 2 fatty changes in the liver

on USG indicating nonalcoholic fatty disease of liver.

The USG pelvis revealed a small uterus of size 26x6 mm with small right and left side ovarian volumes at 1.4ml and 1.7ml respectively. The bone age calculated using the X-Ray of the left hand and the wrist by TW3 RUS atlas was thirteen years and two months. Her karyotype was 46XX,9qh+, which is reported to be a normal variant and isn't associated with any pubertal delay and short stature.

With the above information, a working diagnosis of hypogonadotropic hypogonadism with growth hormone deficiency was made. An LHRH stimulation test was performed which showed a positive response indicating a normally functioning pituitary gland.

	0 HOUR	1 HOUR	4 HOURS
FSH (mIU/ml)	3.85	7.79	17.35
LH (mIU/ml)	0.45	8.14	9.72

Treatment was started with Growth Hormone, low dose Estrogen and anti-obesity drugs with counselling on diet and exercise. This resulted in a gain in height of 4.8 cm in the span of 6 months. The breast development improved to Tanner stage 3. The effect on uterus and gonads was positive. The uterine size increased to 51x29x13mm. The right and left ovarian volume increased to 2.24ml and 1.82 ml respectively. Further, LHRH stimulation test after 3 months revealed an enhanced response than before indicating increase in the functioning of gonadotropes in the pituitary.

	0 HOUR	1 HOUR	4 HOURS
FSH (mIU/ml)	2.22	30.08	35.99
LH (mIU/ml)	0.31	43.03	31.60

To conclude, the above case highlights the role of growth hormone in puberty and need of multi-disciplinary approach involving a paediatric endocrinologist, a nutritionist in the management of a complex problem of short stature and delayed puberty in young girls. Maintaining growth charts in growing children will help pick up these potential correctable problems well before the permanent damage is done. The team approach will result in a complete development of the child with good height and proper reproductive maturity.

Twin Anaemia Polycythemia Sequence: A case discussion

Akshatha Sharma

Consultant, Apollo Centre for Fetal Medicine

A 29 year old primigravida was referred to our centre

in view of Monochorionic Diamniotic Twins with discordance in the amniotic fluid at 15weeks 5 days. Her previous history was unremarkable and her first trimester screening was low risk for aneuploidies with no discordance in the Nuchal translucency/CRL/Ductus venosus.

On the scan,the Deepest Vertical Pool for both the twins were 7cm/3cm and the umbilical artery flows showed positive diastolic flow. We counselled her that this did not yet fit the criteria for the polyhydramnios/ oligohydramnios sequence of Twin Twin Transfusion Syndrome(TTTS). This could remain stable or worsen to advanced Twin Twin Transfusion syndrome(TTTS) in 15% of the cases. A rescan was arranged in a week's time.

At 16weeks 5 days,the amniotic fluid discordancy had increased to 10cm/1.4 cm with absent bladder in the donor. The Dopplers were normal for both twins. This qualified for a classification of Quinteiro's Stage II Twin Twin Transfusion Syndrome. The couple were counselled for Laser Photocoagulation of the anastomosing vessels (risks of PPROM / miscarriage / Twin anaemia polycythemia sequence) vs expectant management (Perinatal mortality reported upto 90%). The couple opted for Laser Photocoagulation which was performed uneventfully. Five large A-V anastomoses were coagulated (Solomon Technique). On Day 2 postprocedure, the ex-donor started showing signs of improvement with appearance of the bladder and improvement of the deepest vertical pool(3cm) suggestive of successful resolution of TTTS. A follow up was arranged weekly.

At the 19 weeks follow up,both bladders were well seen alongwith equalisation of the fluid in both the sacs. However on Doppler insonation, the Middle Cerebral Artery PSV for the ex recipient and ex donor showed discrepancy (>1.5 MoMs vs <1 MoMrespectively). This was indicative of development of Twin Anaemia Polycythemia Sequence(TAPS) which is a known complication in 14% of post-laser cases. We counselled the couple that this could resolve spontaneously in a small percentage of cases or usually progress to further stages of TAPS. The couple agreed for an expectant management for another week when the scan(at 20 weeks) revealed progression of TAPS to Stage 2(MCA PSV >2 MoMs/ <0.5 MoMs).

Counselling for TAPS

The couple was counselled that TAPS has a heterogeneous presentation with poor documentation of its course in literature. This usually occurs due to miniscule (<1mm) AV anastomoses that remain uncoagulated during the primary laser that are present along the margins of the placenta that make their visibility difficult. This leads to a slow selective transfusion of red blood cells(not plasma) from the ex-recipient to the ex-donor causing anaemia in one twin and polycythemia

in the other. Severe TAPS can cause mortality or even poor neurodevelopmental outcomes(upto 20%). The further options available to us were Re-Laser (ideal), selective feticide, Intrauterine transfusion of the anaemic twin either: either umbilical vein transfusion or intraperitoneal transfusion(symptomatic treatment), partial exchange transfusion of the polycythemic twin with transfusion of the anaemic twin. However, the couple opted for a selective feticide if the identification of the miniscule anastomoses was difficult.

At the procedure, fetoscopy was first done in an attempt to identify the miniscule anastomoses however no obvious anastomoses were identified. A decision of Bipolar cord coagulation of the anaemic twin was taken which was performed uneventfully.

Currently, the fetus is 24 weeks with growth on the 50th centile,amniotic fluid and fetal Dopplers normal. She is now planned for a growth scan every 4 weeks with a plan of delivery at 36-37 weeks.

This case emphasises the need for strict post operative follow up protocol and counselling the patient about the possible complications postoperatively. Although infrequent, knowledge and identification of Twin Anaemia Polycythemia Sequence leads to appropriate intervention before the development of hydrops or progression of the disease.

Unilateral Vulvar Edema after Operative Laparoscopy

Lalita Badhwar¹, Shayista Nabi², Sukriti³

¹Sr. Consultant Gynec Laparoscopic Surgery, ²Sr Resident ObGyn, ³DNB student, Department of ObGyn, IP Apollo Hospitals, New Delhi

Introduction

Vulvar edema after laparoscopic surgery is an uncommon complication. We present an unusual case of Unilateral vulvar edema after 48 hours of laparoscopic left ovarian cystectomy.

Case Summary

A 17 year old nulligravida girl presented with intermittent lower abdominal pain for last 6 months. Clinical and ultrasound examination was suggestive of left adnexal cystic mass 18 x15 cm with a provisional diagnosis of endometrioma. After evaluation, she was scheduled for elective laparoscopic cystectomy.

At the operation, a central 10 mm port was created at the umbilicus after creating pneumoperitoneum and telescope introduced. Two Ipsilateral Accessory ports were made; one in the left lower flank and another left para umbilical. No supra pubic port was made. No

extraperitoneal gas insufflation was done.

On laparoscopic examination, Adhesions were present between left ovarian cyst and sigmoid colon and with left infundibulopelvic ligament. A large left ovarian cyst 20x20 cms with three loculi suggestive of endometriotic cyst was seen. Left tube was edematous and stretched over the cyst. In addition, surface endometriotic implants were present on right ovary and peritoneum. Pouch of Douglas was obliterated by adhesions. During adhesiolysis, cyst was opened and around 850 ml of thick chocolate colored fluid poured out. Ovarian cystectomy was done. No adhesion barrier was used.

During her postoperative stay patient was discharged in satisfactory condition after 24 hours. After 48 hours of surgery, patient developed vulvar discomfort. There was no voiding difficulty reported. On examination, profound vulvar swelling involving the entire left labium majus and minus was noted. There was no evidence of cellulitis.

A tight bandage and Magnesium sulphate dressing was applied and she was given bed rest, ice packs, anti inflammatory medication, and antibiotics. Since there was no voiding difficulty, patient was not catheterised.

Complete resolution of edema was achieved in three days and patient was discharged in a comfortable condition.

Discussion

Laparoscopic surgery has several advantages, including shorter operative time, smaller scars, faster recovery and decreased adhesion formation. Most complications related to laparoscopic surgery occur during abdominal

access, but other complications can occur related to abdominal insufflation and tissue dissection.

Vulvar edema has been reported especially in cases in which adhesion barrier solution was used. Escape of the irrigation fluid either intraoperatively or post operatively dissecting downwards subcutaneously to the vulva is believed to be the cause of edema. Pados et al. showed that a tract originating in a suprapubic puncture site and fluid dissecting subcutaneously to the most dependent vulvar area by the force of gravity can result in vulval edema. However the exact mechanism remains unclear.

A case of vulvar edema were reported in 2003 after laparoscopic presacral neurectomy associated with chylous ascites Second look laparoscopy revealed a leak in the presacral area was located which was successfully coagulated.

There is no uniform treatment for this condition. Conservative management in the form of ice packs, bed rest, analgesics, and catheterization is empirical but effective. Antibiotics probably need not be given. Hospitalization may be required in case of voiding difficulties.

Conclusion

Vulvar edema after laparoscopic surgery is an unpredictable rare complication whose pathogenesis is unclear. The condition is managed conservatively, however further studies are required to explain the relationship between vulvar edema and laparoscopic surgery.



Save the Dates

First Announcement

40th

Annual Conference of Association of Obstetricians & Gynaecologists of Delhi (AOGD)

Date: 24th & 25th November, 2018

Venue: India Habitat Centre



