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Welcoming....

Our New Patrons

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Dr. Manjula Anagani
Dr. Nilesh Ramakant Shinde
Dr. Rajalaxmi Walavalkar
Dr. Sasmita Swair
Dr. Siddhartha Chatterjee
Dr. Sripriya Pragasam
Dr. Sudhaa Sharma

Our New Life Members

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Dr. Akhil Saxena
Dr. Anupama Sethi Arora
Dr. Asha Anil Baxi
Dr. B. D. Parsewar
Dr. B. Sandhya Rani
Dr. Bela Jayesh Zaveri
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Dr. Kavitha Senthil
Dr. Mary Anne Raja
Dr. Mohan T. Shenoy
Dr. Mrs. Noorunnisa Bashir Ahmed Kotwal
Dr. Partha Bhattacharya
Dr. Pinky Shah
Dr. Pooja Chetan Ghorpade
Dr. R. Nirupama
Dr. Rakesh Pratap Khuteta
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Dr. Ruchika Garg
Dr. S. M. Sredive
Dr. Sabahat Rasool
Dr. Sarla Nihlani
Dr. Satishkumar Manmohan Sajanwala
Dr. Seenu Garg
Dr. Sheela Prakash Paknikar
Dr. Sudhir Naik
Dr. Susan William
Dr. Sushila Khuteta
Dr. T. Hema
Dr. V. Sita Rama Raju

Congratulations
Dr. Duru Shah for taking over as the President of Indian Society of Assisted Reproduction (ISAR) on 21st April, 2017.
We wish you a year full of academic excellence!
Editorial

Dear Friends,

When I decided to name the PCOS Newsletter “PANDORA” it originated from “Pandora’s Box” which is a well-known phrase for an action which may be very simple, but as you get deeper and deeper into it, it gets more and more detrimental – it’s a never ending situation with far reaching negative consequences!

In Greek mythology, Pandora was the first woman created by the Gods, on the instructions of the Greek God Zeus. Pandora was created as “the beautiful evil” woman after humans stole the gift of fire from Prometheus. She was created to give humanity a punishing gift to compensate for the boon (fire) they had stolen. God Zeus commanded Hephaestus to mould her from earth as, a “beautiful evil” whose descendants would torment the human race.

According to the myth, Pandora opened a jar (not a box) out of curiosity releasing all the evils of humanity and she could retain only “Hope” inside the jar once she had closed the lid quickly. So when you open this Newsletter, all the mysteries of PCOS should disappear and our hope remains, that one day we will be able to decipher the enigma called PCOS.

Our last issue for the year 2016 was published in late December 2016 which you must have received in early January 2017. Since then we have had many academic activities, which you will find in this Newsletter and even on the PCOS Website http://www.pcosindia.org/

We also have many exciting forthcoming events, in which I request you to participate wholeheartedly, though we may have smaller numbers of delegates, but believe me, the interactions are just brilliant!

Our “Whatapp groups” which are open to only our members, have some amazing discussions and many queries are sorted out by many of our senior members who contribute their expertise. I thank them for their time, expertise and love to teach.

We have created beautiful Certificates for our members, which you would love to display on your walls. All members have been sent their Membership Numbers and will soon receive their Certificates, if their paperwork is complete. So, please watch out for this precious package which you will soon receive. And if you don’t get it by the middle of May please send us a mail and we will track the package for you.

I welcome you all to the beautiful city of Bengaluru, between 16, 17, 18 June 2017 where we are hosting our Second Annual International Conference of the PCOS Society of India in collaboration with the Androgren Excess and PCOS Society. You will find the details of the conference on our Website and in this Newsletter. Please register at your earliest!

Please also check out our Website for all the archived educational events which are hosted therehttp://www.pcosindia.org/. These include Power Point Slides, Webinars and Lectures, you will enjoy them.

I must thank all our academic contributors especially Prof. B. N. Chakravarty and team who have written a brilliant article on “Is Letrozole Better for Ovulation Induction” and Prof. Fabio Facchinetti who has written an excellent review on “Insulin Sensitizing Properties of Inositol: Experimental Studies” and a beautiful article by Dr. Jayshree Todkar on “PCOS & Obesity”.

I thank my Editorial team for all their help and inputs and Mr. Manoj Purandare from Sun Pharma for offering us an unrestricted educational grant to make this issue possible.

Dr. Duru Shah
Founder President, PCOS Society
Events & Updates

PCOS Symposia – An Update on Surgical Solutions for PCOS

An Update on “Surgical Solutions for PCOS” was organized by The PCOS Society, India, in collaboration with Meril Endosurgery Pvt Ltd on 18th-19th March, 2017 at Meril Academy, Daman. Dr. Duru Shah was the chief convenor.

The conference was structured as 4 sessions over 2 days followed by 3 debates & panel discussion on Bariatric surgery vs. Cosmetic surgery, Laparoscopic vs. Open surgery and OCPs vs. LNG in DUB. The panel discussion was moderated by Dr. Duru Shah and Dr. Madhuri Patil.

This exclusive two-day program was meticulously designed to upgrade and discuss various "Surgical Solutions for PCOS women". The symposia focused on understanding and optimizing the use of various surgical disciplines and imbibing the latest research towards a better quality of life for young girls and women with PCOS.

The topics were focused on the very complicated and vast topic of PCOS and surgical treatment of PCOS. The impact of PCOS on fertility, and the effects of fertility enhancing surgeries in PCOS was extensively discussed.

The 1st day sessions included ‘Fertility Surgeries in PCOS’ & ‘Obesity & Laparoscopic Surgery’. The 2nd day sessions included ‘Difficulties at Hysteroscopic Surgeries’ and ‘PCOS and Obesity’.

International Webinar – PCOS Beyond Boundaries – Focusing on Hyperandrogenism in PCOS

The PCOS Society (India) conducted an International Webinar titled PCOS Beyond Boundaries – Focusing on Hyperandrogenism in PCOS, on 4th March, at Taj Santacruz – Mumbai with support from Bayer Zydus Pharma which connected with 6 webcast centres – Salem, Vizag, Dehradun, Bhubaneshwar, Gurgaon, Patna. Prof. Roy Homburg connected live from Malta and made an extraordinary presentation on PCOS – The Global Conundrum, & was joined by a multispecialty panel of distinguished experts from India – Dr. Duru Shah (Gynaecologist), Dr. Shashank Joshi (Endocrinologist), Dr. Ashwini Bhalerao (Gynaecologist), Dr. Gulrez Tyebkhan (Dermatologist)

290 doctors participated in the Webinar at the 7 centers, with 254 online viewers, and the webinar was rated as very educative and informative.
16th June 2017 – PRE-CONGRESS WORKSHOPS

09.30 am - 01.30 pm – Workshop 1
- Diagnosis of PCOS by USG – What are the new criteria?
- Is ultrasound a good diagnostic method in adolescent PCOS?
- Should Serum AMH replace ultrasound PCO morphology as a diagnostic marker?
- Assessment of ovarian blood flow in PCOS, Does 3D power doppler have any role?
- Discussion
11.30 am - 12.30 pm
- Session III: Monitoring a Fertility cycle
- Should follicle monitoring be done by the Fertility expert/ Radiologist / USG Nurse?
- How should we monitor the follicles and endometrium during a COS cycle by ultrasound?
- How should we assess OHSS by ultrasound, what are the high risk markers?
- Discussion
12.30 pm
- Live Demonstration of Ultrasound in PCOS women

02.30 - 05.30 pm – Workshop 2
- Practical Management of Ovulation Induction in PCOS
- Case-based discussion
- Lean / Obese PCOS
- High AMH, Insulin resistance
- Role of Letrozole for OI in PCOS
- Role of Adjuvants in PCOS
- Which Gonadotropin? Step up or Step down regimen?
- GnRH agonist or antagonist
- Monitoring the Ovulation Induction cycle – USG or USG+ Hormones
- Avoiding Premature LH surge and lutenization during COH
- Role of laparoscopic drilling, ultrasound only protocols for monitoring COS cycle

06.30 - 08.00 pm – Inaugural Lectures
- International guidelines in PCOS
- Interaction
- Adipose tissue dysfunction in PCOS
- Interaction
- Abhiyan PCOS – A consortium for Research, Advocacy and Action
- Interaction
- 08.00 pm – Inauguration
- 08.45 pm onwards – Fun filled Tambola
- 08.45 pm – DINNER

17th June 2017 – Conference Day 1 – Scientific Session I

08.30 - 09.30 am – Session I : Free Papers
- Diagnosis of PCOS
- What are the different Phenotypes of PCOS? Its importance in management
- The role of environmental factors from fetal life to adulthood in PCOS
- ”The thrifty gene” hypothesis— how has the PCOS phenotype survived evolution?
- Discussion
11.30 am - 01.00 pm – Session III : Obesity and PCOS
- Metabolic risk of the ”lean” PCOS women
- Weight loss drugs – How do we select the right formulation?
- When should we suggest Bariatric surgery in PCOS?
- Is snoring in obese women a health concern?
- Discussion
02.00 - 03.00 pm – Session IV : Keynote Address
- Are we telling patients all they need to know about PCOS?
- Role of GWAS in identifying the PCOS genes
03.00 - 04.00 pm
- Session V : Hirsutism and hyperandrogenism
- Does Insulin Resistance (IR) cause hyperandrogenemia (HA) or HA causes IR?
- Medical options for women with Acne and Hirsutism
- Cosmetic options
- Discussion
04.00 - 05.00 pm
- Session VI: Current update on Inositols
- Pharmacology and Mode of action
- Inositol and Reproductive Function
- Current evidence for its use in Infertility and Pregnancy
- Discussion
05.30 - 06.30 pm – Session VII: The Great Controversies
- Controversy 1
- Should Metformin be continued in pregnancy?
- Yes 
- No
- Controversy 2
- Is PCOS is associated with a higher pregnancy loss?
- Yes 
- No
06.30 - 07.30 pm
- Session VIII : Stump the Experts – Interesting cases
- Menstrual dysfunction in PCOS women
- Insulin resistance and hyperandrogenemia
- Gestational Diabetes Mellitus
- Obstetric complications other than GDM
- 07.30 pm – General Body Meeting of The PCOS Society (India)
- 08.30 pm – COCKTAILS & DINNER with Entertainment

18th June 2017 – Conference Day 2 – Scientific Session II

08.00 - 09.00 am
- Round Tables with development of Algorithms
  1. Vitamin D deficiency and PCOS
  2. Management of acne, pigmentation
  3. Increased lipids
  4. GDM
09.00 - 10.30 am – Session IX : Lifestyle Modification – Does it impact Fertility?
- How do lifestyle changes help in PCOS?
- Do Metformin and Inositols help?
- Exercise in PCOS
- Nutrition in PCOS and role of anti-inflammatory diet
- Discussion
10.30 - 11.30 am
- Session X : PCOS and Assisted Reproduction
- Does PCOS compromise the oocyte and embryo quality or the endometrium?
- Should “freeze all” be a strategy in all PCOS women undergoing IVF?
- Does pre implantation genetic screening (PGS) followed by elective single embryo transfer (eSET) have a role in women with PCOS?
- Discussion
12.00 noon -01.00 pm
- Session XI : Surgical options in PCOS
- Ovarian Drilling – Current Status
- Endometrial Polyps
- Other ovarian pathologies associated with PCOS
- Discussion
01.00 - 02.00 pm – Session XII: Long-term effect of PCOS
- COS and Cancer Risk
- Dysfunctional Uterine Bleeding
- Liver and PCOS: what we really know?
- Discussion
02.00 pm – Valedictory
02.15 pm – COOKIES & DINNER with Entertainment

International Faculty
- Anuja Dokras, USA
- Enrico Carmina, Italy
- Helena Teede, Australia
- Joop Laven, Netherlands
- Richard Legro, USA

National Faculty
- Abha Majumdar
- Ameet Patki
- Anita Soni
- Arti Prasad
- Anurmozi Ramanjan
- Bina Vasan
- Chandler Lula
- Chitra Ganesh
- Devika Gunaseela
- Duru Shah
- Ganapathi B.
- Gita Arjun
- Guerez Tyebkhun
- Jyotika Desai
- Kamini Rao
- Karthi Bansal
- Kedar Ganja
- Korula George
- M. G. Bhat
- Madhuri Peti
- Minabhushan
- Govindarajan
- Nalini Mahajan
- Padmarekha Jirge
- Paul PG
- Piyaa Ballani
- Pratap Kumar
- Priit Venkatesh
- Ragini Agrawal
- Rana Vaidya
- Reeta Billanyaid
- Rekha Sheth
- S. Suresh
- Sujata Misra
- Sumeet Agrawal
- Shashank Joshi
- Sheela Mane
- Shilpa Joshi
- Shobha Gudi
- Shobhana Patted
- Smita Mahale
- Sonia Malik
- Sujata Kulkarni
Insulin Sensitizing Properties of Inositol: Experimental Studies

Dr. Fabio Facchinetti
Chairman, Unit of Obstetrics and Gynecology, Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Italy

Daniela Menichini
Researcher, Department of Maternal Fetal Medicine, University of Texas Health Science Centre at Houston, USA.

Introduction

'Insolitor' refers to a group of molecules called 'stereoisomers' of inositol. They exist in nine possible forms, all composed of the same basic structure, named myo-, scylo-, epic-, D-chiro-, L-chiro, neo-allo-, cis-, and muco-isomers. Inositol sugars comprise of a cyclic six-carbon structure with one hydroxyl group at each carbon. Among the isomers, Myo-Inositol (MI) is the most abundant, naturally present in animal and plant cells, either in its free form or as a bound-component of phospholipids or inositol phosphates. It is a precursor for phosphorylated compounds known as phosphoinositides, which are involved in signal transduction, including diacylglycerol and inositol phosphoinositides, which are involved in signal transduction, including diacylglycerol and diacylglycerol kinase activity. MI in models of hyperlipidemic and insulin-resistant diabetes suggests that MI could play an effective role in glucose disposal into insulin-resistant diabetic rats receiving MI showed significant reductions in fasting blood glucose & plasma insulin level when compared with controls. The inositol treatment significantly normalized the hyperglycemia-induced biochemical abnormalities in insulin-resistant diabetic rats suggesting that MI could play an effective role in glucose disposal into adipose tissue by insulin-dependent signaling cascade mechanism; hence it could be used in the treatment of obesity-associated T2DM.2

2. Experimental studies conducted in pregnancy

A mixture of MI and DCI has recently been tested in pregnant obese mouse model and in pregnant metabolic-like syndrome mouse model obtained from the offspring born to hypertensive dams lacking endothelial nitric oxide synthase, fed with HFD. The treatment with combined inositol during pregnancy improved blood pressure, glucose levels at the glucose tolerance test, and leptin levels in pregnant dams with metabolic-like syndrome phenotype but not in obese pregnant dams. In addition, inositol treatment resulted in lower gestational weight gain in the obese but not in the metabolic-like syndrome pregnant dams. MI has also been clinically experimented on pregnant overweight women with the aim of reducing gestational diabetes mellitus (GDM) rate. An open-label randomized trial evaluated the effectiveness of the supplementation of MI or placebo from the first trimester to delivery in pregnant overweight non-obese women. The incidence of GDM was significantly reduced in the MI group compared to the placebo group, driving to the conclusion that MI supplementation, since early pregnancy, reduces GDM incidence in overweight non-obese women. MI and DCI in a ratio corresponding to their concentrations in normal and pathological states evidenced the suitability of such an integrated approach, by combining MI and DCI in a ratio corresponding to their concentrations in normal and pathological states.

2.1 Experimental studies: Polycystic ovary syndrome (PCOS)

PCOS is an endocrine disorder affecting up to 10-15% of women in reproductive age, mainly causing infertility. Insulin resistance (IR) plays a key role in such syndrome. Recently, MI and DCI have shown to be an efficient and safe alternative in PCOS management, as both inositol isomers can counteract downstream consequences of insulin resistance. Yet, whereas DCI contributes in mediating insulin activity mainly on non-ovarian tissues, MI displays specific effects on ovary, chiefly by modulating glucose metabolism and FSH-signaling. Moreover, MI may also improve ovarian functions by modulating steroid metabolism through non-insulin-dependent pathways. As DCI and MI activity likely involves different biological mechanisms, both inositol isomers can be synergistically integrated for their action, by combining MI and DCI in a ratio corresponding to their concentrations in normal and pathological states.

Continued on page 11
Is Letrozole Better for Ovulation Induction?

Introduction
Over the past five decades, clomiphene citrate (CC) continues to be the first line treatment primarily for ovulation induction and also for ovulation augmentation in unexplained infertility and in intrauterine insemination (IUI) cycles. However, it is reported that 20-25% of women fail to ovulate due to CC-resistance. In view of this, administration of gonadotropins is considered to be the conventional option in such cases. Though use of gonadotropins is highly effective, it is associated with inevitable risk of multiple pregnancies and ovarian hyperstimulation in a significant proportion of women. As an alternative management to gonadotropins, use of laparoscopic ovarian drilling (LOD) in CC-resistant women has also been advocated. Addition of CC with Gonadotropins (FSH/hMG) helps in decreasing the dose of total amount of gonadotropins required for optimum stimulation and makes it more cost-effective in women who fail to respond to only CC treatment. Acceptable pregnancy rates with CC and sequential hMG ovulation induction protocol in IUI following previous CC and IUI treatment failure have also been reported. However, supra-physiological level of estradiol (E2) is an undesirable consequence of both CC and gonadotropin stimulation. Apart from risk of hyperstimulation and multiple pregnancies, adverse effects of supra-physiological level of E2 have been observed at several levels. These are – Dysynchrony between endometrium and embryo maturation during ‘implantation window’ period, abnormal expression of endometrial pinopodes, defective endometrial estrogen – progesterone receptors, abnormal endometrial blood flow and abnormal integral expression. These are some of the reasons for low pregnancy rate in spite of having good ovulatory response following CC induction in anovulatory infertility.

These limitations motivated researchers to find out an alternative drug which would be less expensive than gonadotropins and at the same time safe, simple and equally if not more effective than clomiphene. Letrozole was considered to be an alternative acceptable molecule.

How and Why Letrozole?
In women with intact hypothalamic-pituitary-ovarian axis, the commonest cause of anovulation is Polycystic Ovarian Syndrome (PCOS). One of the significant causes of anovulation in PCOS women is ‘static’ (not pulsatile) elevated or normal level of oestrogen. Static level of estrogen through ‘negative feed-back’ mechanism on ‘hypothalamic-pituitary (HP) axis’ inhibits adequate release of pituitary FSH. Low (not absent) level of FSH results in inadequate growth and development of follicles, – not allowing them to reach maturity and ovulation. At the same time, tonic elevated level of oestrogen through ‘positive feed-back’ effect on HP axis results in release of static elevated ‘tonic’ level of LH. There is no LH surge and therefore anovulation. Aromatase inhibitors (letrozole) by inhibiting oestrogen synthesis temporarily release hypothalamic-pituitary block by tonic elevated oestrogen thereby normalizing fluctuating (and not tonic) release of pituitary FSH which helps in restoration of normal ovulatory cycle. Therefore, letrozole was considered to be an effective drug for induction of ovulation.

Literature review:
Several research groups have studied the new group of drugs (aromatase inhibitors) for ovulation induction in the past few years. Letrozole, a potent and highly specific nonsteroidal aromatase inhibitor, has been observed to be effective in inducing ovulation in anovulatory and ovulatory infertile women with inadequate response to CC. Initially, letrozole was primarily used as a potent reversible oral aromatase inhibitor which acts a chemotherapeutic agent in postmenopausal women with metastatic breast cancer. Being a chemotherapeutic agent, when the drug was used for ovulation induction, concerns were raised about teratogenic effect on oocyte and embryo. Moreover, the resulting hypo-estrogenic may have adverse impact on bone mineral metabolism leading to osteoporosis. The other controversy relating to the use of letrozole as a first-line agent, before CC has been used, is based on the fact that in normo-gonadotropin women, aromatase inhibition is likely to be effective only when baseline estradiol is elevated. The cut-off level of the elevated baseline estrogen is not yet demarcated. Hence use of letrozole as a primary ovulation-inducing drug replacing clomiphene warrants further investigation. An abstract presented at American Society for Reproductive Medicine (ASRM) meeting 2005 regarding increased teratogenic risk of cardiac malformations with letrozole and other safety concerns eventually led to the ban on this drug in India in 2011. Nevertheless, there is an increased concern on the factuality of the observation due to the shortcomings and biases of this study.

In the later years, various studies indicated that letrozole is not associated with increased teratogenic risk. Our earlier study showed that the overall rate of congenital malformations among children born to mothers who conceived naturally or after letrozole or CC treatment was observed to be comparable. Our group has conducted one of the largest-ever randomized clinical trials to explore the efficacy of letrozole in ovulation induction on 1387 infertile PCOS women who failed to conceive with CC treatment. This study showed that letrozole appears to be a suitable ovulation inducing agent in polycystic ovary syndrome (PCOS) women with CC failure and is found to be most effective when baseline E2 level >60 pg/ml. It is well known that infertility itself is a risk factor and is associated with increased malformation risk as compared to the general population. Several published studies, both controlled and non controlled, comparing letrozole with CC alone or in combination with gonadotropins confirm the effectiveness of letrozole as an ovulation inducing agent. Based on these various reports, Government of India, Ministry of Health and Family Welfare removed the ban on use of letrozole as ovulation induction agent.

Evolution of aromatase inhibitors for clinical use
Aromatase inhibitors suppress estrogen production by inhibiting the conversion of androgens to estrogens. Letrozole, the drug commonly used in clinical practice, has been developed following extensive trial through three generations of aromatase inhibitors. Third generation aromatase inhibitors like letrozole and anastrozole have been a great leap forward in the treatment of breast cancer. Their clinical efficacy, excellent tolerability and safety profile compare favourably with that of tamoxifen, which has been the cornerstone of endocrine therapy for years.

Concept leading to the use of letrozole for induction of ovulation
The goal of ovulation induction is to induce folliculocentric development and subsequent ovulation in anovulatory infertile women. As discussed in previous paragraphs, anovulation in PCOS or any normogonadotropin anovulatory cycle is due to the block of hypothalamic receptors by static elevated supraphysiological level of oestradiol, which is preventing the release of pulsatile lutetinizing hormone-releasing hormone (LHRH). Decline in static elevated oestradiol level can help in restoration of...
synchronized and pulsatile LHRR release. Antiestrogenic effect of letrozole was the concept behind using it for ovulation induction. This was first reported in literature by Mitwally et al., in anovulatory women resistant to ovulation induction by CC.

**Need of an alternative drug for ovulation induction other than clomiphene citrate**
Several drawbacks with CC had been the reason for lookout for an alternative ovulation inducing agent in certain cases. CC remains bound with oestrogen receptors for 60 days because of its long half life. In case CC fails to induce ovulation or establish pregnancy, other ovulation inducing drugs cannot be initiated before 60 days. It is thought that dose of 150 mg or more will confer no benefit. CC induces ovulation in 70-85% of patients while only 20-40% will conceive. The pregnancy rate per cycle is around 10-20%. About 20-25% anovulatory women are clomiphene resistant.

CC has unfavourable effects on endometrial thickness and cervical mucus due to its antiestrogenic effect. The incidence of miscarriage after CC therapy has been reported to be about 23.6%. It has been shown that with prolonged CC use, along with low endometrial thickness, there is also decreased uterine blood flow during early luteal and peri-implantation phase. There have been evidences suggesting that supra-physiological level of circulating estrogens, allowing hypotalamus to release effective synchronized pulsatile LHRR, thereby leading to LH surge and ovulation.

**Letrozole**

Letrozole causes direct inhibition of oestrogen synthesis thereby allowing follicle-stimulating hormone (FSH) to induce active folliculogenesis. This hypo-estrogenic state is quickly reversible due to the short half-life of letrozole (45 hours). There is no antioestrogenic effect on endometrium. Also there is temporary elevation of testosterone to an optimum level which is beneficial as it increases the follicular sensitivity to gonadotropin.

Excess levels of androgen cause detrimental effects whereas a very low level of testosterone impairs follicular development.

**Common features in mechanism of action of CC and letrozole**

Though the drugs act in different ways, there are some common features in their mechanism of actions. These are: (a) Release of hypotalamus from negative tonic feedback effect of static normal or elevated level of oestrogen (b) Allowing release of pulsatile gonadotropin-releasing hormone (GnRH) (c) FSH & LH ratio is synchronized (d) LH surge effective for ovulation. These have been illustrated in Fig-1 &Fig-2.

**Ovulation induction in anovulatory women with PCOS**

Letrozole versus CC in PCOS women has been tested in several randomized trials. However, the efficacy of letrozole in ovulation induction remains unclear. One of the largest randomized controlled trials conducted in our institute comparing efficacy of letrozole with continuous gonadotropins and CC-gonadotropin combination for ovulation induction in 1387 PCOS women after clomiphene citrate failure concluded that the ovulation and pregnancy rate with letrozole was significantly higher with letrozole compared to CC-rFSH combination (79.30% vs 56.95%, p value <0.001 respectively) (14). Also there was a significantly lower cycle cancellation rate with letrozole compared to CC-rFSH (20.70% vs 43.05%, p value <0.0001) respectively). Another group had reported comparable pregnancy rate with letrozole and CC-hMG therapy in a pilot study. An analysis of four early randomized studies observed a significantly higher pregnancy and delivery rate in women treated with aromatase inhibitor compared with CC. Nonetheless, the trials involved were heterogeneous with a limited number of patients.

A recent well-designed double blind multicentre randomized control trial comparing letrozole versus clomiphene for infertile PCOS women has concluded that letrozole was associated with higher live birth and ovulation rates. Therefore, letrozole is considered to be superior than CC as a treatment for anovulatory infertility in women with PCOS. Similar findings were observed by other studies. A meta-analysis published in 2015 analysed 4999 ovulation cycles (2455 with letrozole, 2544 with CC) indicated that live birth and pregnancy rates were higher in patients with PCOS following treatment with letrozole as compared to CC. However, there was no difference in ovulation rate/cycle, miscarriage rate or multiple pregnancy rate between the two drugs.

**Ovulation induction/stimulation in unexplained infertility**

Aromatase inhibitors are recommended as an alternative drug to CC in women with unexplained infertility, either alone or with gonadotrophins. Nonetheless, it is likely to be less efficacious compared with treatment in PCOS women. Letrozole results in lesser number of mature follicles (mono-ovulation) in comparison to CC because it has less anti-estrogenic effects in the later part of follicular phase. Thus, it may not be the first choice in patients with unexplained infertility. A meta-analysis of seven randomized control trials showed comparable clinical pregnancy rates between aromatase inhibitor and CC in women with unexplained infertility. These findings are in good agreement with another large trial where no statistically significant difference was observed between 100 mg of CC versus 5 mg of letrozole in terms of clinical pregnancy rate in unexplained infertility. A recent large multicentre trial on 900 women with unexplained infertility concluded that letrozole resulted in lower frequency of multiple pregnancies but also lower live birth rates as compared to gonadotropins. However, when letrozole was compared to clomiphene alone, pregnancy rates were similar.

**Safety concerns with letrozole**

Concerns had been raised regarding the use of letrozole for ovulation induction, as it might interrupt the normal aromatase function in tissues during early fetal development and can be potentially teratogenic. This issue was discussed in the Annual Meeting of the American Society for Reproductive Medicine in 2005. An abstract presentation by the authors discussing the use of letrozole for
infertility treatment may be associated with a higher risk of congenital cardiac and bone malformations in the newborns. Following this, Novartis Pharmaceuticals, the company that developed letrozole for breast cancer treatment, issued a warning to infertility clinics asserting that it does not advocate letrozole use for infertility treatment. In a critical review from the Ministry of Health and Family Welfare, India issued a directive to suspend the use of letrozole in infertility women with immediate effect citing concerns regarding its safety. A study analyzing 911 newborns born after infertility treatment with either CC or letrozole found no difference in overall rates of major and minor congenital malformations between the two groups. In a recent retrospective trial from Asian sub-continent analyzing 646 women, congenital malformations were found to be comparable following natural conception, letrozole and CC. Most recent trial by Tatum et al. (2017) reported that no increase in the risk of major congenital anomalies or adverse pregnancy or neonatal outcomes was observed in letrozole treated women compared with natural cycles in women undergoing ART. Considering these reports, Indian Health Ministry has recently removed the ban on letrozole for use in infertility. Therefore, letrozole may be considered as a safe option for ovulation induction.

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**Introduction**

Since its original description in 1935, obesity has been recognized as a common feature of the Polycystic Ovary Syndrome (PCOS). Moreover, obesity exacerbates many of the reproductive and metabolic abnormalities associated with PCOS. This review explores the available data on the mechanisms of this association.

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health. People are generally considered obese when their body mass index (BMI), a measurement obtained by dividing a person’s weight in kg by the square of the person’s height in metres, is over 30 kg/m², with the range 25-30 kg/m² defined as overweight.

**Pathophysiology**

PCOS has metabolic characteristics that include prominent defects in insulin and β-cell function that confer a substantially increased risk for glucose intolerance and type 2 diabetes. Furthermore, the metabolic abnormalities associated with PCOS, such as β-cell dysfunction and type 2 diabetes, have heritable components in families of women with PCOS. To date, the genes responsible for PCOS have not been clearly identified. Considering the close association between PCOS and obesity, it is likely that similar or interrelated genes may also predispose to obesity in affected women. No doubt environmental factors (high-caloric diets and reduced exercise) also play a major role in the high prevalence of obesity in women with PCOS1. Insulin resistance is a predominant finding in PCOS. Insulin-mediated glucose disposal, reflecting mainly insulin action on skeletal muscle, is decreased by 35-40% in women with PCOS compared to weight comparable reproductively normal women. This defect is significantly correlated to obesity. Hepatic insulin resistance, characterized by both increased post absorptive glucose production and reduced sensitivity to insulin, is present in obese women with PCOS2.

Fasting insulin levels are increased in PCOS & are more pronounced in women with PCOS who have a first-degree relative with type 2 diabetes. Under normal circumstances, the relation between insulin secretion and sensitivity is constant so that changes in insulin sensitivity are accompanied by reciprocal changes in insulin secretion that maintain normal glucose tolerance; this relationship is known as the “disposition index.” Women with PCOS have a lower disposition index compared to weight-matched reproductively normal women3. PCOS is associated with high rates of glucose intolerance resulting from defects in insulin action and β-cell function. Detection of glucose abnormalities in women with PCOS is best performed by means of glucose tolerance testing, since fasting glucose levels may be normal despite presence of glucose intolerance4-6.

**Treatment for PCOS**

PCOS treatment starts with a proper diagnosis. Treatments are then chosen based on a woman’s symptoms, age and future pregnancy plans. Treatment for PCOS is not effective unless the baseline metabolic disorders-Obesity and Insulin Resistance are dealt with scientifically. As per the scientific and clinical evidence, these are the treatments options for Obesity/Adiposity and the Insulin Resistance:

1. **Supervised Diet and Exercise Modifications** are a must in this treatment. But may not be effective enough alone7.

2. **Pharmacotherapy** – Apart from Metformin, inositol and Orlistat, no pharmacotherapy is really available to treat adiposity/obesity/ metabolic syndrome.

3. **Bariatric Surgery in PCOS** – 10% of women world wide are suffering from PCOS, and will seek help for gynaecological disorders or body image. Many such women are at a risk of Metabolic Syndrome, predisposed to glucose abnormalities ie. DM, Dyslipidemia, Cardiovascular diseases. Metabolic Syndrome (MS) and obesity co-exist. Bariatric surgery can be an effective and safe means of treatment for obese women with PCOS. Bariatric surgery can prevent or reverse Metabolic Syndrome associated with PCOS, leading to reproductive benefits8.

4. PCOS treatment requires combination of medical therapy, psychological support, lifestyle modifications and should include bariatric surgery as a firm treatment modality, whereever indicated. Bariatric surgeries help obese women in terms of improved fertility index, improved interpersonal relationships & sexual behavior, prevention of Gestational Diabetes & Pregnancy Induced Hypertension. Women with morbid obesity, who are infertile secondary to PCOS, may have a new surgical option in the form of bariatric surgery. Studies report that 100 % of the morbidly obese women who were diagnosed with PCOS-related infertility became pregnant within three years following Bariatric Surgery.

**Methods of Bariatric Surgery**

Bariatric surgery has been available for decades. Most procedures are now performed laparoscopically. Three most common procedures performed are: 1. Laparoscopic adjustable gastric banding (LAGB) 2. Laparoscopic roux-en-Y gastric bypass (RYGB) 3. Laparoscopic sleeve gastrectomy (LSG)

Weight loss for each procedure increases subsequently in each of the first 3 years post-operatively.

Decreased surgical time, shorter hospital stay and postoperatively in pre-menopausal women with MS. Bariatric procedures showed improved insulin values proportional to changes in BMI.

The effects on hypertension have been shown to be independent of the magnitude of weight loss. Reproductive age women fitting the profile of PCOS are included in many of the studies. Most women regained normal menstrual function and most had documented spontaneous ovulation. Patients had significant improvement in hirsutism & androgen profiles post Bariatric Surgery. Follow up for more than 2 years showed that all women resumed normal menstrual cycles, half had resolution of hirsutism and HbA1C decreased from 8.2% to 5.1%. Dyslipidemia, hypertension and diabetes mellitus almost completely resolved. Interestingly, women became pregnant spontaneously after surgery. 78% of women saw improvement in MS and 48% showed improvement in PCOS specifically with regards to menstrual cycles, fertility and/or hirsutism. PCOS presents a unique challenge since many obese PCOS women are adolescents. Although patients and physicians may at first be wary of a young patient considering surgical weight loss, these patients have an important opportunity. Bariatric surgery may actually provide primary prevention of coronary artery disease, eliminate MS and cause meaningful, long term reduction in morbidity and mortality. Young women with PCOS show evidence of atherosclerosis by abnormal carotid intima media thickness measurement and the prevalence of diabetes mellitus before the age of 50 is exceptionally high and estimated at 3-4 times the general population prevalence9.

Reproductive concerns may also lead PCOS women with MS to consider bariatric surgery. The relationship between PCOS, obesity and infertility has been documented for many years. Known effects include anovulation, miscarriage, impairment in folliculogenesis and altered endometrial receptivity. Risks in pregnant woman with PCOS & MS are high, namely diabetes, pre-eclampsia, growth disorders, higher rates of cesarean delivery, higher maternal mortality and increase risks of metabolic disease in their children. Bariatric surgery in reproductive age women has been shown to decrease menstrual irregularities. PCOS women have less hyper-androgenism post LH and FSH levels have been reported to increase after surgery. On a more functional level, ovulatory function measured by luteal LH and progesterone secretion improved postoperatively, although levels were still below normal values. Additionally, leptin levels decrease after bariatric surgery, reflecting improved reproductive metabolic status. These changes certainly would suggest improved reproductive function. Women already take pregnancy into consideration when electing for bariatric surgery. Although women tend to seek medical care for menstrual irregularities and hirsutism, this encounter offers a chance for evaluation, education and risk prevention of MS. Lifestyle modification and treatment of risk factors are appropriate and even necessary for long term control. Bariatric surgery is a powerful tool that should not be overlooked simply because a woman is young or presents with PCOS and MS rather than diabetes mellitus, myocardial
Infarction and severe chronic hypertension. In our experience of Bariatric surgery since 2003, we have treated more than 60% women patients for overweight/Obesity and related co morbidity. Out of this population, around 70% belonged to the reproductive age. The BMI range was between 28 to 70 kg/m2. 42% of these women had PCOS and infertility as the primary concern. All of them showed improved ovulatory function and fertility index after Bariatric surgery.

References

Inulin Sensitizing Properties of Inositol: Experimental Studies

Such effects are mediated by specific changes in placenta pathways that improve intrauterine environment in humans and mouse, resulting finally in the interruption of the epigenetic vicious cycle which transfer maternal metabolic and cardiovascular diseases to the offspring. Moreover, inositol counteracts the downstream consequences of insulin resistance in women affected by PCOS, ameliorating the fertility by decreasing the need of ovulation hyper stimulation and increasing the pregnancy rate.

Lastly, inositol supplementation from the first trimester of pregnancy demonstrated to have a role in reducing the incidence of pregnancy in overweight and obese women.

However, larger studies, in double-blind trials, including a more heterogeneous population would be necessary, to confirm the previous results for women with GDM, PCOS or post-menopausal and to test a possible application for a more generalized population of subjects already presenting an insulin resistance or at risk of developing one because of genetic predisposition.

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Insulin Sensitizing Properties of Inositol: Experimental Studies

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Symposium on PCOS – Science to Practice

One day Symposium on “PCOS – Science to Practice” was organized by the Guwahati Obstetrics & Gynaecological Society under the aegis of PCOS Society of India on the 11th December 2016 at Hotel Landmark, Guwahati. Dr. R. K. Talukdar was the chief convenor, & Dr. Gitanjali Deka was the organizing secretary.

Experts in the fields of gynaecology, infertility, dermatology and endocrinology spoke on the various aspect of the multifaceted condition of PCOS. Drs. Rekha Sheth, Saswati S. Chaudhary, Uma Kaima Saikia & Ashok Bhuyan were the keynote speakers. The symposium was attended by 140 gynaecologists and was spread over 6 sessions, which focused on Basics in PCOS, Infertility & PCOS, Evidence Based treatment, PCOS & Pregnancy, Health risks of PCOS and Drugs in PCOS.

The attendees expressed their interest to seek more information through CMEs in the diagnosis & phenotypes of PCOS, IIV in PCOS and etiopathogenesis of PCOS.

Events & Updates

Symposium on PCOS – Science to Practice
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- Chromium picolinate ensures higher ovulation rate than Metformin⁵