IFS CONVERSATIONS

Volume 1 : September, 2016

INDIAN FERTILITY SOCIETY

INDEX

INSULIN SENSITIZERS

MYTHS & FACTS

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MESSAGE FROM THE PRESIDENT DESK

Dear Friends,

It is indeed a great privilege and pleasure for me to write this message for the "IFS Conversation" Volume I, July 2016 issue. Polycystic Ovary Syndrome (PCOS) is the most common endocrinological disorder among reproductive age group women. While dietary and lifestyle modifications are the mandatory first line measures to control this disorder, the insulin sensitizers, due to their undisputed potential to ameliorate the effects of insulin resistance and compensatory hyper insulinaemia, commonly found in PCOS women, have generated a great deal of interest, specially over last decade. However, there still remains a lot of controversy over the exact role of insulin sensitizers in improving live birth rates and minimizing the incidence of complications during pregnancy and delivery. Dr Bharati Dhorepatil and her team have addressed the "Myths and facts" about Insulin sensitizers in this issue, in a most comprehensive and brilliant manner. I am sure, the readers will find it very informative and helpful in their clinical practice.

The "IFS Conversation" also showcases the various recent academic activities conducted by our extremely enthusiastic and committed members spread over 15 chapters across India. Several of our members have also made IFS very proud through their remarkable achievements at the recent ESHRE Annual Meeting held at Helsinki on 3-6 July. My heartiest congratulations are conveyed to each one of you! Our latest endeavor- the e-bulletin "NEXUS" has been proudly launched in June 2016. It is aimed to bridge the gap between ART clinicians and embryologists and provide latest concepts on quality control, basic IUI and IVF techniques and lab protocols. The "NEXUS" has been possible due to valued partnership of IFS with "ORIGIO India Private Limited", initiated through the innovative idea and hard work of our joint secretary - Dr Pankaj Talwar. The inaugural volume focused exclusively on "IUI- bolts & nuts" and next issue is already under preparation titled as "Semen Analysis: trouble shooting". The great opportunity to participate in the 22nd IFFS World Congress, due to be held on 21-25 September 2016 is just round the corner! Those who have not registered yet, are gently reminded to visit the website www.iffs2016.com and register immediately! We look forward to meeting each one of you at this unique event at India Expo Centre, Greater Noida (Delhi NCR).

I congratulate Dr Bharati Dhorepatil and her entire team for their excellent hard work and dedication to plan and prepare this news bulletin within a very short time and wish all readers a very rewarding and pleasant reading. Your feedback and suggestions are always most welcome and sincerely requested. Please do visit our website www.indianfertilitysociety.org for regular updates on our forthcoming courses, CMEs and conferences.

Warms Regards and best wishes

Dr. Sohani Verma
President- IFS

MESSAGE FROM THE SECRETARY GENERAL'S DESK

Dear Friends,

It gives me immense pleasure to bring to all IFS members the next edition of "IFS Conversation" IFS newsletter. I would like to congratulate the editorial board, the authors and contributors for their efforts in continuing the spread of information and keeping us all updated with recent advances in this ever evolving field of ART. Since its inception Indian fertility society has taken and fulfilled the responsibility of disseminating knowledge and scientific content through conferences, CME, work shops and train young embryologists and Infertility specialist through fellowship programs. This bulletin is a step forward in this direction. With the increasing incidence of PCOS and metabolic syndrome, management of insulin resistance is a dilemma for all clinicians, this edition shall throw light on role of insulin sensitizers, dispel myths and clarify its indications in background of available scientific evidence.

This edition also introduces 12 Special Interest Groups, created for focused and dedicated interactions in various sub categories of ART. Interested IFS members are welcome to join these SIG's. Looking forward to enthusiastic participation in International Federation of Fertility Societies (IFFS) - 22nd World Congress, to be held on 21st to 25th September 2016, at Noida.

With Warm Regards,

Dr. K D Nayar
Secretary General-IFS

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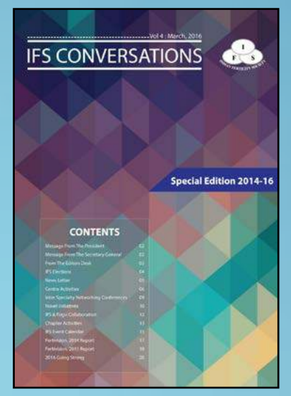
MESSAGE FROM THE EDITOR'S DESK



Dear all,

At the outset we would like to thank you all for giving us the opportunity to serve IFS organization through this conversation as Editors.

This is the 1st volume of year 2016 under the able leadership of Dr Sohani Verma, focusing on Insulin Sensitizers and all official communications for all our members across.

We are opening one column from this year as Members Opinion..Pl share your opinions and suggestions for the better outcome.

Every great achievement, is once an impossibility, just like a raw seed. It never know its true potential in the form it exists. Its only when its sits deeply, and prepares for change we see its journey from - Roots to Fruits.

Lets take a closer look at 'the seeds'..

Any remarkable victory that has ever happened, been spoken or invented began first with an idea. Many people are constantly getting ideas. Their mind is producing many new thoughts on a regular basis. This is incredible because that means that the seeds for great things are right there in the soil of our minds and hearts.

Unfortunately, all too often we do not let those seeds grow. Instead we dismiss the idea. We will never know, but I wonder who it was that first thought of the light bulb, but dismissed the idea. I wonder who it was that first saw an Aeroplane in his or her mind's eye, but dismissed the idea. Who was it that thought up the way to run computers but allowed the seed to slip away?

Let these seeds grow! Do not dismiss any idea as a bad one immediately. Write your ideas down. Look at them for a week or a year. Brew over them. Consider them. Let them GROW. In the end you may need to dismiss them, but not before you give them a chance to grow into something incredible that may change your life, your family, your business, your community or your world.

If you let your ideas grow, you will surely see many great things happen in your life.

Happy Reading and Meet you all in the next Conversation.

Dr. Surveen Ghumman
Joint Editor-IFS

Dr. Bharati Dhorepatil
Editor-IFS

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CERTIFIED TRUE COPY OF THE RESOLUTION PASSED BY GOVERNING COUNCIL OF INDIAN FERTILITY SOCIETY AT ITS DULY CONVENED MEETING AND AT WHICH A PROPER QUORUM (18 MEMBERS) WAS PRESENT HELD ON 17.05.16 AT 5 PM.

Sub- News Report in "Hindustan Times New Delhi" dated May 10, 2016

"IVF helps Septuagenarians become first time parents"

With reference to the recently published above mentioned news report ,the undersigned, on behalf of the Governing Council of Indian Fertility Society (IFS), wish to convey our firm and undivided opinion, that IFS strongly condemns the use of ART/ IVF technology in such patients. We fully agree and support the recommendations by ICMR that IVF treatment shall be limited to only up to 50/55 years age group couple at the maximum. The view is endorsed due to well acknowledged serious health risks to the mother as well as due to potential serious impact on physical, psychological and social well being of the child to be born out of such treatment, apart from the question of financial security.

The IFS strongly rejects all justification whatsoever to support such practices, which will go down in the history, as a dark spot against all good work being carried out by thousands of infertility practitioners in our country. This highly controversial case however raises several very uncomfortable and disturbing questions which simply cannot be brushed aside under the carpet, putting all blame on a particular doctor or a single IVF centre as no law has been broken by them and as proclaimed by them IVF treatment was carried out in good faith for their patient and that particular section of society they work for. As concerned responsible citizens, if we really want to get to the root cause of this problem, we ourselves and the society as a whole, must address following questions-

1. What drives a 72 years old woman to opt for the tremendous hardship of pregnancy, childbirth and months of sleepless nights which most of the 30 year something will consider too exhaustive and harder than any other full time job in the world?
2. What drives a septuagenarian couple to subject themselves to more than 2 years of stressful infertility treatment and make a 24 x 7 commitment, when their most other counterparts would be enjoying a relaxed, tension free life with just enough energy to cope with minimal essential physical activity? Is it the simple greed or the pressure to have a baby, especially on women, is so huge that everything else in comparison appears easier? And who is to be blamed for it- the woman, her husband or the society?
3. Why is the risk of losing their share of inherited money / property so important to this septuagenarian couple to justify their decision for such drastic steps at this phase of their lives? Is it not the inability of the state / country to provide financial security and dignity to all its senior citizens and the absence of same is one of the main reasons for this obsession of many couples to have a child at no matter how much are the risks?
4. Most importantly - why is there still no ART Regulation Law despite ICMR thinking about it since 2005 (ICMR guidelines 2005)? During this 11 year period, IVF clinics have increased hundred folds in number but the pace at which our law making system has moved over the same duration is most astonishing.

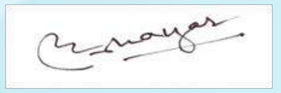
The same clinic earlier made headlines all over the world in 2006 with the news of a 70 year old woman giving birth to an IVF baby, but nothing material has been done in effect to have prevented such practices.

It is not just a question of one couple, one baby or one doctor, there must be thousands of other similar couples in same vulnerable circumstances getting lured into undergoing years of infertility treatment which they ignorantly assume , will end all miseries of their lives. Those who do get pregnant, then face the challenge of putting their own and their baby's lives at considerable risks and suffering.

The law making authorities should have woken up long ago. The most important undeniable need of the hour is for the government authorities to sit together with the IVF service providers and finalize the draft ART Bill 2014 to make it practical as well as efficient enough to protect and take care of the interests of all stake holders and implement it as a law on a most urgent priority.

Meanwhile, the doctors need to realize that IVF technology is not the magical cure for all sins and ills of the society. IFS recommends all its members to strictly refrain themselves from succumbing to the emotional blackmail and psychological pressures put upon them by the patients and refuse all such treatments, which are clearly and totally against interests of the society.

Dr Sohani Verma
President- IFS



Dr K D Nayar
Secretary General- IFS

IFS FERTIVISION 2015-2016

HANDING OVER THE BATON

From Dr. Sonia Malik to Dr. Sohani Verma

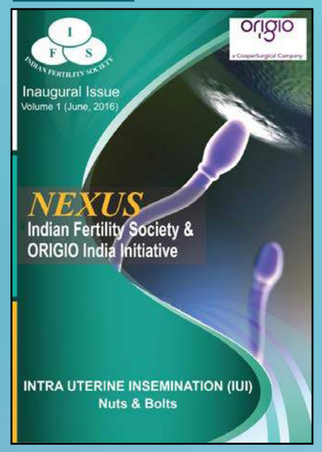
From Dr. Sudha Prasad to Dr. KD Nayar

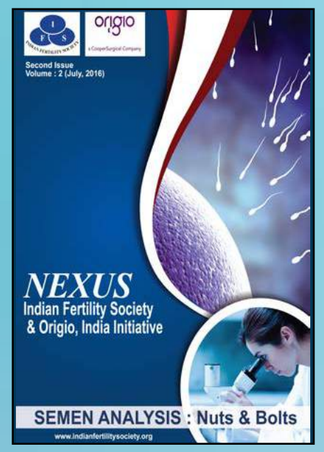
FLAGSHIP PROGRAMME OF IFS

1. Embryology Preparatory Certification Course for ESHRE Exam
2. Clinical Embroyology
3. Clinical ART

IFS JOURNAL

NEXUS





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ROLE OF INSULIN SENSITISERS IN FERTILITY OUTCOMES IN PATIENTS OF POLYCYSTIC OVARIAN DISEASE (REVIEW ARTICLE)

INTRODUCTION

Polycystic ovary syndrome (PCOS), also called hyperandrogenic anovulation (HA)(1) or Stein–Leventhal syndrome,(2) is a set of symptoms due to a hormone imbalance in women.(3) Symptoms include: irregular or no menstrual periods, heavy periods, excess body or facial hair, acne, pelvic pain, infertility, and patches of thick dark velvety skin.(4) Associated conditions include, Type 2 Diabetes, Obesity, obstructive sleep Apnea, Heart Disease, Mood Disorders, and, Endometrial Cancers.(3)

PCOS is due to a combination of genetic and environmental factors.[5] Risk factors include obesity, not enough physical exercise, and a family history of someone with the condition.[6] Diagnosis is based on two of the following three findings: no ovulation, high androgen levels, and ovarian cysts.[3] Cysts may be detectable by ultrasound. Other conditions that produce similar symptoms include adrenal hyperplasia,hyperthyroidism and hyperprolactinemia[7] PCOS has no cure.[8] Treatment may involve lifestyle changes such as weight loss and exercise. Birth Control Pills may help with improving the regularity of periods, excess hair, and acne. Metformin and antiandrogens may also help. Other typical acne treatments and hair removal techniques may be used.[9] Efforts to improve fertility include weight loss, Clomiphene, or metformin. In- Vitro Fertilization is used by some in whom other measures are not effective.[10]

PCOS is the most common endocrine disorder among women between the ages of 18 and 44.[11] It affects approximately 5% to 10% of this age group.[6] It is one of the leading causes of poor fertility.[3] The earliest known description of what is now recognized as PCOS date from 1721 in Italy.[12]

SIGNS AND SYMPTOMS

Common symptoms of PCOS include the following:

- Menstrual Disorders: PCOS mostly produces oligomenorhoea (few menstrual periods) or amenorhoea (no menstrual periods), but other types of menstrual disorders may also occur.[11][13]
- Infertility (13) : This is generally results directly from chronic anovulation (lack of ovulation).[11]
- High Levels of Circulating masculinizing Hormones: The most common signs are acne and Hirsuitism(male pattern of hair growth), but it may producehypermenorhoea(heavy and prolonged menstrual periods, Androgenis Alopecia (increase hair thinning or diffuse hair loss), or other symptoms.[11][14] Approximately three-quarters of people with PCOS (by the diagnostic criteria of NIH/NICHD 1990) have evidence of Hyperandrogenemia.[15]
- Metabolic Syndrome:[13] This appears as a tendency towards Central Obesity and other symptoms associated with Insulin Resistance11] Serum Insulin, insulin resistance, and Homocysteinelevels are higher in women with PCOS.[16]

Asians affected by PCOS are less likely to develop hirsutism than those of other ethnic backgrounds.[17]

CAUSE

PCOS is a heterogeneous disorder of uncertain cause.[13][18][19] There is strong evidence that it is a Genetic Disease. Such evidence includes the familial clustering of cases, greater concordance in monozygotic compared with dizygotic twins and heritability of endocrine and metabolic features of PCOS.[5][18][19]

The genetic component appears to be inherited in an autosomal dominant fashion with high genetic penetrance but variableexpessivityin females; this means that each child has a 50% chance of inheriting the predisposing genetic variant(s) from a parent, and, if a daughter receives the variant(s), the daughter will have the disease to some extent.[19][20][21][22] The genetic variant(s) can be inherited from either the father or the mother, and can be passed along to both sons (who may be asymptomatic carriers or may have symptoms such as early baldness and/or excessive hair) and daughters, who will show signs of PCOS.[20][22] The allele appears to manifest itself at least partially via heightened androgen levels secreted by ovarian follicle theca cells from women with the allele.[21] The exact gene affected has not yet been identified.[5][19][23]

The severity of PCOS symptoms appears to be largely determined by factors such as obesity.[5][11]

PCOS has some aspects of a metabolic disorder, since its symptoms are partly reversible. Even though considered as a gynecological problem, PCOS consists of 28 clinical symptoms.

Even though the name suggests that the ovaries are the cornerstone of disease pathology, cysts are a symptom instead of the cause of the disease. Some symptoms of PCOS will persist even if both ovaries are removed; the disease can appear even if cysts are absent. Since its first description by Stein and Leventhal in 1935, the criteria of diagnosis, symptoms, and causative factors are subject to debate. Gynecologists often see it as a gynecological problem, with the ovaries being the primary organ affected. However, recent insights show a multi system disorder, with the primary problem lying in hormonal regulation in the hypothalamus, with the involvement of many organs. The name PCOD is used when there is ultrasonographic evidence. The term PCOS is used since there is a wide spectrum of symptoms possible, and cysts in the ovaries are seen only in 15% of people.[24]

PCOS may be related to or exacerbated by exposures during the prenatal period, epigenetic factors, environmental impacts (especially industrial endocrine disruptors[25] such as Bisphenol A and certain drugs) and the increasing rates of obesity.[25][26][27][28][29][30][31]

DEFINITION

The following definitions are commonly used:

1.NIH

In 1990 a consensus workshop sponsored by the NIH/NIHCD suggested that a person has PCOS if she has all of the following:[33]

- Oligoovulation
- Signs of androgen excess (clinical or biochemical)
- Exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism

2.Rotterdam

In 2003 a consensus workshop sponsored by ESHRE/ARSM in ROTTERDAM indicated PCOS to be present if any 2 out of 3 criteria are met, in the absence of other entities that might cause these findings[11][34][35]

- Oligoand/or anovulation
- Excess androgen activity
- Polycystic ovaries (by Gynecological Ultrasound)

The Rotterdam definition is wider, including many more women, the most notable ones being women without androgen excess. Critics say that findings obtained from the study of women with androgen excess cannot necessarily be extrapolated to women without androgen excess.[36][37]

3.Androgen Excess PCOS Society

In 2006, the Androgen Excess PCOS Society suggested a tightening of the diagnostic criteria to all of the following:[11]

- Excess androgen activity
- Oligoovulation/anovulation and/or polycystic ovaries
- Exclusion of other entities that would cause excess androgen activity

STANDARD DIAGNOSTIC ASSESSMENTS

- History-taking, specifically for menstrual pattern, obesity, hirsutism and acne. A Clinical Prediction rule found that these four questions can diagnose PCOS with a sensitivity of 77.1% (95% confidence Interval [CI] 62.7%–88.0%) and a specificity of 93.8% (95% CI 82.8%–98.7%).[38]
- Gynecological Ultrasonography specifically looking for small ovarian follicles. These are believed to be the result of disturbed ovarian function with failed ovulation, reflected by the infrequent or absent menstruation that is typical of the condition. In a normal menstrual cycle, one egg is released from a dominant follicle – in essence, a cyst that bursts to release the egg. After ovulation, the follicle remnant is transformed into a Progestrone-producing Corpus Luteumwhich shrinks and disappears after approximately 12–14 days. In PCOS, there is a so-called "follicular arrest"; i.e., several follicles develop to a size of 5–7 mm, but not further. No single follicle reaches the preovulatory size (16 mm or more). According to the Rotterdam criteria, 12 or more small follicles should be seen in an ovary on ultrasound examination.

[33] More recent research suggests that there should be at least 25 follicles in an ovary to designate it as having polycystic ovarian morphology (PCOM) in women aged 18–35 years.[39] The follicles may be oriented in the periphery, giving the appearance of a 'string of pearls'.[40] If a high resolution transvaginal ultrasonography machine is not available, an ovarian volume of at least 10 ml is regarded as an acceptable definition of having polycystic ovarian morphology instead of follicle count.[39]

- Laproscopicexamination may reveal a thickened, smooth, pearl-white outer surface of the ovary. (This would usually be an incidental finding if laparoscopy were performed for some other reason, as it would not be routine to examine the ovaries in this way to confirm a diagnosis of PCOS.)
- Serum (blood) levels of androgens (male hormones), including Androstenidione and Testostronemay be elevated.[11]. Dehydroepi and rostenidione sulphate (DHEAS) levels above 700-800 µg/dL are highly suggestive of adrenal dysfunction because DHEA-S is made exclusively by the adrenal glands.[41][42] The free testosterone level is thought to be the best measure,[42][43] with ~60% of PCOS patients demonstrating supranormal levels.[15] The Free Androgen Index (FAI) of the ratio of testosterone to Sex Hormone Binding Globulin (SHBG) is high[11][42] and is meant to be a predictor of free testosterone, but is a poor parameter for this and is no better than testosterone alone as a marker for PCOS,[44] possibly because FAI is correlated with the degree of obesity.[45]

Some other blood tests are suggestive but not diagnostic. The ratio of LH to FSH, when measured in international units, is elevated in women with PCOS. Common cut-offs to designate abnormally high LH/FSH ratios are 2:1[46] or 3:1[42] as tested on Day 3 of the menstrual cycle. The pattern is not very sensitive; a ratio of 2:1 or higher was present in less than 50% of women with PCOS in one study.[46] There are often low levels of sex hormone binding globulin,[42] in particular among obese or overweight women.[

Anti – Mullerian Hormone (AMH) is increased in PCOS, and may become part of its diagnostic criteria.[47][48]

DIAGNOSTIC CRITERIA FOR THE INSULIN RESISTANCE SYNDROME IN WOMEN

Any three or more of the following:

Waist circumference >88 cm
Triglycerides ≥ 150 mg/dLa
HDL-cholesterol <50 mg/dLb
Blood pressure ≥130/85
Fasting glucose ≥110 mg/dLc

a To convert triglycerides to mmol/L multiply by 0.0112.
b To convert HDL-cholesterol to mmol/L multiply by 0.0256.
c To convert glucose to mmol/L multiply by 0.055.
HDL, high density lipoprotein.(49)

DIFFERENTIAL DIAGNOSIS OF PCOS (49)

Table 3

Differential diagnoses and screening tests.

Diagnosis	Laboratory test
Pregnancy	Pregnancy test
Hypothyroidism	TSH
Hyperprolactinemia	Prolactin
Late-onset CAH	17-hydroxyprogesterone[a]
Ovarian tumor	Total testosterone[b]
Hyperthecosis	Total testosterone
Adrenal tumor	DHEA-S[b]
Cushingís syndrome	24-hour urine free cortisol

LABORATORY EVALUATION OF INSULIN RESISTANCE OR GLUCOSE INTOLERANCE (50)

Test	Interpretation
Fasting Glucose/ insulin ratio	<4.5 in obese, euglycemic, non-Hispanic white adult polycystic ovarian syndrome patients[14] (<7.0 in adolescents[13]) consistent with insulin resistance.
75 g oral glucose tolerance test	**Normal :** 2 hour glucose ≥140 mg/dL **Impaired glucose tolerance:** 2 hour glucose 140-199 mg/dL **Diabetes:** 2 hour glucose >200 mg/dL

MANAGEMENT OF PCOS

The management of PCOS can be broken down into four components, three of which are acute issues (management of irregular menses, control of Hirsuitism and treatment of infertility). The last however requires strict attention in order to prevent long term sequelae of Diabetes Mellitus, Endometrial Cancer, and Cardiovasular Disease.

LIFESTYLE MODIFICATIONS/ WEIGHT LOSS

Lifestyle modifications and weight loss play a tremendous role in achieving significant improvement in the symptoms and signs of PCOS but also help to prevent the long term sequelae of the disease.

In a study by Kiddy et al, about 40% of obese women with PCOS and metabolic Syndrome with BMI = 34 kg/mg2 who lost more than 5% of their body weight with lifestyle changes and diet achieved spontaneous pregnancy.(51)

A more recent trial compared the effects of an energy-restricted diet (~1400 kcal/day) through either a low or high protein diet in 28 obese (mean BMI ~ 37 kg/m2) PCOS subjects over 12 weeks.(52) Subjects were also advised to increase exercise to a minimum of 3 times weekly though no information was reported as to the actual duration and/or intensity achieved. Average weight loss was 7.5% (with abdominal fat decreasing 12.5%), and 3 of the 20 subjects actively trying to conceive did so (two in the high and one in the low-protein group) for a rate of 15%. Thus, lifestyle modification needs to be stressed in the treatment of infertility. A 3 to 6 month trial of aggressive lifestyle modification may be a prudent first step before considering an insulin sensitizer. However, many patients will have difficulty in achieving weight loss.

The following were the results of the randomized control study

Weight Loss in PCOS: Results of RCT

	Control (n=84)	Intervention (n=87)
Weight loss (kg)	1.3 (0.2)	4.7 (0.3)*
Pregnancies at 18months	18 (21.4%)	53 (61%)*
Miscarriage	3 (16.6%)	6 (11.3%)
ART pregnancies	9%	37%*
Spontaneous pregnancies	11%	24%*

* p<0.001 — Moran et al, 2003

ROLE OF INSULIN SENSITIZING AGENTS - METFORMIN

The initial report of metformin in the treatment of PCOS by Velazquez et al. in 1994 described three spontaneous pregnancies (~11% of subjects).(53) Since that time, a number of other studies have been completed assessing metformin's role in the treatment of PCOS. The primary outcomes of these studies were the effects on parameters of IR, hyperandrogenemia, and improvements in menstrual function and ovulation. Many of these studies were small, involving approximately 20 patients each, but in the five trials describing spontaneous pregnancies, the rate was between 5% and 18%.(54,55-58) A recent study by Heard et al. involved 48 anovulatory PCOS patients (mean age of 29.9 years and BMI of 28.7 kg/m2) enrolled for 15 months.(57) Metformin was started at 500 mg twice daily and increased to three times daily if ovulation did not occur by 6 weeks, and clomiphene was added 6 weeks later as needed.

Normalization of menstrual cycles and ovulation occurred in 19/48 subjects (40%) on metformin alone, and 15 of them (79%) became pregnant. Nearly 75% of these pregnancies on metformin alone occurred within 3 months of starting the medication. The addition of low dose clomiphene (50 mg) resulted in five additional pregnancies.(59) Similar rates of ovulation (40%) were seen with metformin alone in obese subjects (mean BMI ~32 kg/m2), while the addition of clomiphene increased that rate to 89%.(56)The use of clomiphene alone resulted in only an 11.5% ovulation rate. Pregnancies were not reported. Lastly, in clomiphene-resistant PCOS patients, metformin pre-treatment increased conception rates from 7% to 55%.(60)The use of metformin also improves the outcome of more advanced infertility therapies. When used for 1 month prior to ovulation induction with FSH, metformin reduced the risk of ovarian hyperstimulation.(61)As well, metformin improves fertilization and pregnancy rates in women with PCOS undergoing in vitro fertilization.(62)Thus, in the setting of infertility, metformin therapy should likely be continued for as long as fertility efforts are ongoing, even if it "fails" initially.

As mentioned, once pregnancy is achieved in PCOS patients, the first-trimester miscarriage rate is 3-fold higher than that of normal women.(50)Recently, metformin therapy continued throughout pregnancy has been shown to reduce this risk of early pregnancy loss. In a retrospective study of women who became pregnant on metformin and continued it throughout pregnancy, the rate of early pregnancy loss was 8.8% compared to 41.9% of women who were not on the drug.(63)In a prospective pilot study, Glueck et al. have reported on 19 women receiving metformin during their pregnancy to date.(64)Fifty-eight percent have had normal live births, 32% have ongoing pregnancies beyond the first trimester, and 10.5% had first-trimester miscarriages. No birth defects occurred.(64) This study will eventually include 125 women with PCOS. However, metformin is not approved for use in ovulation induction or during pregnancy. It is pregnancy category B.

CONCLUSION

Polycystic ovarian syndrome(PCOS) is one of the most common endocrine disorders affecting women and is characterized by a combination of Hyper-Androgenism , Chronic Anovulation, Insulin resistance and Metabolic Syndrome.

PCOS has no cure.[8] Treatment may involve lifestyle changes such as weight loss and exercise.

Lifestyle modifications and weight loss play a tremendous role in achieving significant improvement in the symptoms and signs of PCOS but also help to prevent the long term sequelae of the disease.

Individual manifestations of this disorder can be treated but it is necessary to focus on prevention of long term effects of PCOS and metabolic Syndrome.

Myoinositol (MI) and D-Chiroinositol (DCI) have been proven to be effective in the PCOS treatment by improving Insulin resistance, Serum Androgen levels and many features of Metabolic Syndrome. However, DCI alone, mostly when it is administered at high dosage, negatively affects the oocyte quality, whereas MI/DCI in a combination reproducing the plasma physiological ratio of (40:1), represents a promising alternative in achieving better clinical results, by counteracting PCOS and both systemic and at ovarian level.

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METFORMIN USE IN PCOS

Metformin and other insulin sensitizers have been used for nearly the last two decades in PCOS in order to decrease the insulin resistance in these patients. However, its use in ovulation induction has been controversial. While it was initially accepted as a first line treatment in anovulatory PCOS, ACOG guidelines (2003)placed it as the second drug to be added to clomiphene if clomiphene fails as a first line induction agent. The Canadian guideline of 2010 stated that metformin combined with clomiphene citrate may increase ovulation rates and pregnancy rates but does not significantly improve the live birth rate over that of clomiphene citrate alone. Metformin may be added to clomiphene citrate in women with clomiphene resistance who are older and who have visceral obesity.

Soon a Cochrane review (2012) indicated that metformin was not effective in inducing ovulation alone or in relation to clomiphene but it was capable of increasing the pregnancy outcome. It concluded that the role of metformin in improving reproductive outcomes in women with PCOS appears to be limited.

The Thessaloniki ASRM/ESHRE guidelines (2008) further emphasized the same and restricted its use to PCOS patients where there was a glucose intolerance noted. It also indicated that it was helpful in reducing the incidence of OHSS and missed abortion but did not recommend its use in pregnancy.

India did not have any guidelines till the IFS issued its first guideline on PCOS management in 2014. Metformin has therefore been used unrestrictedly in the country for all PCOS phenotypes. However, the guideline recommends its use in PCOS and advises not to use it in pregnancy.

The coming years have found many new articles that support its use for modifying the PCOS phenotype prior to infertility treatment, improving oocyte quality and also highly recommend it for the prevention of OHSS. This review article by Aboubakr Mohamed Elnashar from the Middle East Fertility Society journal beautifully illustrates the current status of metformin in the management of PCOS.

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PCO Special Interest Group

PCO Special Interest Group has been created to escalate recent advancement in PCOS.

Convener: Dr Sonia Malik **Co- convener :** Dr Bharti Dhorpatil

IFS members can send their short CV to IFS Secretariat to join this SIG and participate in latest updates in PCOS/ Infertility Management.

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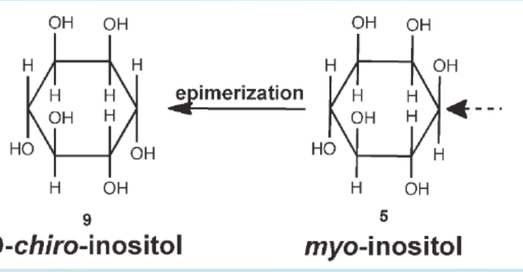
MYOINOSITOL IN PCOS – HOPE OR HYPE?

Recent market is flooded with Inositol with the pharma promoting the product in various forms and various combinations as well. Particular emphasis is made on the use of Inositol in women with PCOS. Is Inositol truly a wonder molecule? Or, is it just another molecule in the block that is now under the limelight and likely to fade in the next couple of years?

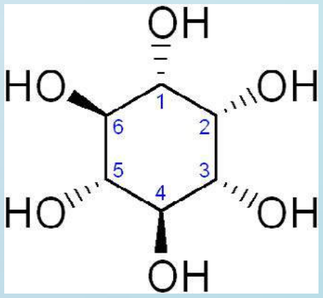
Here, we make a brief attempt to give you an insight into Inositol and how it can impact reproductive medicine.

Myo-inositol is not a new discovery. In 1850 Johanes Joseph Scherer (1814-1869) isolated it from the muscle and named it Inositol [Greek –in fiber, -ose carbohydrate, -ite ester, -ol alcohol)1. Subsequently, several scientists studied the role of Inositol in body functions for many years.

In 1988 Larner et al identified that the two inositol stereoisomers, Myo-inositol(MI) and D-chiro-inositol (DCI), are chemical mediators of insulin, acting through different mechanisms. D-chiro- inositol (DCI) is synthetized by an epimerase that converts Myo-inositol (MI) into D-chiro-inositol.



Myoinositol (MI) is considered by some as one of the B Complex vitamins and is synthesized from Glucose in the Liver and Kidneys. It is Hexahydroxylcyclohexane and has nine stereoisomers.



Human adults consume approximately 1 g of inositol per day in different biochemical forms. It has one tenth the sweetness of sugar It is present naturally in many fruits, nuts, cereals in the form of hexa phosphates and phytates[2].

In the animal tissues it is present in the form of phospholipids. Since it is water soluble any excess is excreted through the kidneys and hence does not lead to toxicity.

MECHANISM OF ACTION

Inositol is present in the cell membrane as Phosphatidyl MI. Phospholipase C converts these into the two second messengers, inositol 1,4,5-trisphosphate (InsP3) and diacylglycerol (DAG). These second messengers operate throughout the life of a cell to regulate a variety of cellular processes including gametogenesis, fertilization, cell proliferation and development amongst various others3.

One of the important actions of Inositol is in Insulin pathway. Insulin-signaling pathways involve inositol phosphoglycans (IPGs). When insulin binds to its receptor, two distinct IPGs are released by the hydrolysis of Inositol lipids (glycosylphosphatidylinositol) located in the cell membrane. These IPGs enter inside the cells and activate key pathways that control the oxidative and non- oxidative metabolism of glucose.

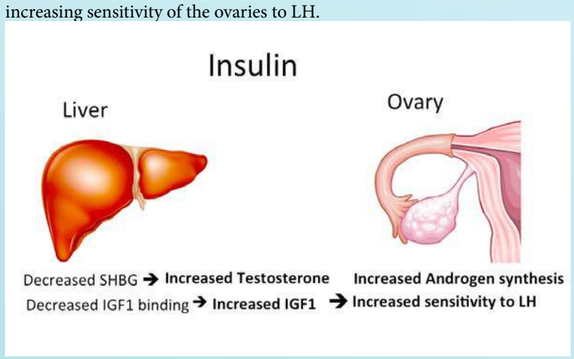
DIFFERENT ROLES OF MI AND DCI

Both MI and DCI have insulin sensitizing effect and reduce the levels of insulin in the blood. However, MI and DCI have different action within the cells. MI increases the entry of glucose into the cell making it available as a substrate for various processes. DCI on the other hand, increases the intracellular accumulation of glucose and is responsible for glycogen synthesis.

Myo-inositol	D-Chiro Inositol
Acts both on ovary and peripheral tissues	Acts at peripheral tissues
Increases cell glucose intake	Stimulates glycogen synthesis
mproves insulin sensitivity & reduces hyperinsulinemia	Improves insulin sensitivity & reduces hyperinsulinemia
Improves oocyte quality	Reduces risk of metabolic syn-drome
Reduces the amount of FSH during IVF cycles	
Improves IVF results	

THE INOSITOL LINK TO PCOS

Joseph Larner conducted studies and showed that the DCI content in the urine of monkeys and humans with Type II Diabetes was increased4. This was linked to Insulin resistance. It was around this time that clinical features of PCOS was linked to Insulin resistance. Insulin resistance lead to hyperinsulinemia and this lead to reproductive dysfunction5. Hyperinsulinemia has a direct effect on the ovaries. Acting on the theca cells of the ovary, insulin promotes androgen synthesis. Also, increased insulin levels in the liver leads to a reduction of circulating levels of sex hormone-binding globulin, resulting in increased circulating free testosterone. Apart from this, insulin induces a reduction of the synthesis of insulin- like growth factors binding protein-1, giving rise to an increase of circulating IGF-1 and increasing sensitivity of the ovaries to LH.



Once Insulin Resistance was linked to PCOS, studies were conducted to find the role of Inositol in PCOS. It was realized that insulin resistance could be a result of impaired signaling of its intracellular messenger pathways. A defect in the Inositolphosphoglycans (IPGs) second messenger pathway opened a new horizon in the clinical management of PCOS.

Having established the link between Inositol and PCOS, studies were now directed towards righting the problem of insulin resistance in PCOS by supplementing Inositol. The first one to be tried was D-Chiro Inositol (DCI).

DCI supplementation to women with obese PCOS was tried and the results were promising. Clinical trials with 1200mg of DCI in the management of obese PCOS was found to be effective not only in improving glucose tolerance, but also in reducing serum free testosterone levels, blood pressure and plasma triglyceride levels compared to placebo6.

In 2002, Nestler and Allan conducted similar trials in lean PCOS and the results were promising with similar results. However, when high doses of DCI were used, the same beneficial effect was not seen. The poor results of DCI supplementation in higher doses while it was effective in lower doses could not be explained. This was disappointing and the enthusiasm of further studies of DCI supplementation reduced.

MYO-INOSITOL (MI) AND FERTILITY

However, several others continued work on the other Inositols. In 1992, Chiu et al7 published their study on the role of MI in IVF. The study reported an elevated level of inositol in serum samples of patients having successful IVF pregnancies, thus indicating a possible involvement of inositol in both the early in vitro phase of IVF and the maintenance of normal embryonic development. Role of MI in follicular maturation was further confirmed when the same group8 studied the MI content in the Follicular fluid of patients who underwent IVF. A total of 53 patients treated with IVF were recruited. Group A with matured and fertilized oocytes showed significantly high levels of MI in follicular fluid compared to Group B which had immature and unfertilized Oocytes indicating that MI is associated with follicular maturation.

EFFECT OF MI ON OOCYTE QUALITY

Oocytes are characterized by high glucose consumption along with the oxidative pathway. When sugar is restricted or unavailable, oocyte quality becomes poor. In PCOS, there is a defect in the transportation of glucose in the oocytes and follicular cells due to down regulation of genes involved in the glucose uptake pathway. Though both DCI and MI are required to perform such function in synergy with insulin, MI seems to play a more important role in oocytes.

To evaluate the effect of MI on oocyte quality in women undergoing ICSI, a study was undertaken9. It was found that the amount of recombinant FSH administered and the number of days of stimulation was significantly reduced in the MI group compared to the placebo group. Further more, in PCOS patients treated with MI and folic acid10, but not folic acid alone, reduced germinal vesicles and degenerated oocytes at ovum pick-up were observed.

INOSITOL IN IRREGULAR MENSTRUATION

Unfer et al, administered MI with Folic acid twice a day for 6months to PCOS women with irregular periods and compared it with Placebo. MI supplementation restored spontaneous menstrual cycles and consequently fertility.

Subsequent studies confirmed11 that daily supplementation of MI in both lean and obese PCOS regularized menstrual cycles, improved hormonal profile and restored ovulation.

Gerli S et al12, conducted a double blind, placebo controlled study to assess the use of MI in treatment of PCOS. Of the 92 patients randomized, 47 received 400 mcg folic acid as placebo, and 45 received MI plus folic acid. The ovulation frequency was significantly ($P < 0.01$) higher in the treated group (25%) compared with the placebo (15%), and the time to first ovulation was significantly ($P < 0.05$) shorter. The effect of MI on follicular maturation was rapid, because the E2 circulating concentration increased over the first week of treatment only in the MI group. A significant increase in circulating high-density lipoprotein, loss of body weight was observed only in the MI group.

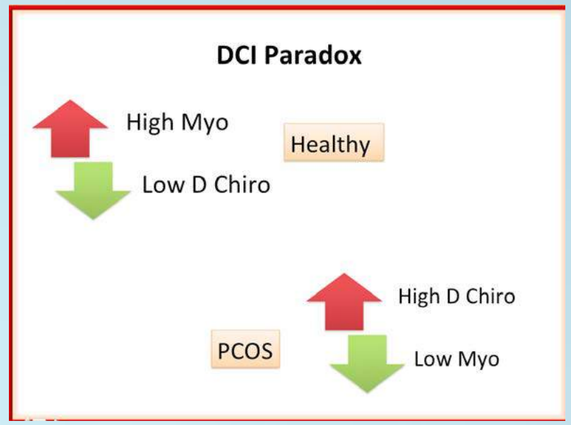
THE DCI PARADOX

Evidence of the beneficial effect of MI on oocyte quality had accumulated. However, it was still unclear why DCI, which was effective in earlier studies, was found to be ineffective in higher doses. To solve this paradox, the effects of MI and DCI on oocyte quality in euglycemic PCOS patients undergoing ICSI were compared13. Results showed that the total number of oocytes retrieved did not differ in the two treatments groups. However, the number of mature oocytes was significantly increased and the number of immature oocytes decreased in the MI compared to the DCI group. The mean number of top quality embryos and the total number of pregnancies were higher in the MI group compared to DCI group.

Why was there a difference between the MI and the DCI groups?

PCOS is associated with Insulin resistance, which is seen in most of the tissues like liver, muscle and fat. Ovaries however remain insulin sensitive. Hyperinsulinemia at the level of ovaries could lead to increased conversion of MI to DCI since the epimerase enzyme responsible for the conversion is insulin dependent. This increased conversion leads to depletion of MI in the follicular cells with consequent impairment of FSH signaling. This could also explain the increased requirement of FSH in the stimulation protocols of PCOS women and the poor oocyte quality.

The levels of MI and DCI were studied in women with PCOS and healthy women. The study demonstrated that follicular fluid from spontaneous cycles of healthy patients contains high concentrations of MI and low concentrations of DCI while in PCOS patients, there was high DCI and low MI. This explains the 'DCI paradox' accordingly to which "ovaries in PCOS patients likely present an enhanced MI to DCI epimerization that causes MI depletion with consequent poor oocyte characteristics of these patients.



This also explains the beneficial effects seen with low doses of DCI but not higher doses. At lower doses, DCI by its peripheral effect reduced insulin levels which lead to decreased conversion of MI to DCI at the ovarian level, decreased androgen levels and improved FSH signaling. At higher doses of DCI, the effect on the ovary was reversed leading to depletion of MI. A combination of MI and DCI rather than only DCI improves IVF outcome. This has been brought out in a study published in 2013 by Sandra Colazingari et al. The combined treatment induced an earlier rescue to normal values than MI alone.

COMPARISON OF MI WITH METFORMIN IN PCOS

A RCT to study the metabolic and hormonal effects of myoinositol vs. metformin in women with polycystic ovary syndrome showed that both decreased body mass index, androgenic features, improved menstrual abnormalities and polycystic ovaries but the level of insulin resistance as measured by fasting insulin and homeostatic model assessment (HOMA) decreased only on treatment with myoinositol14. However, metformin intake is associated with a significantly high incidence of gastrointestinal disturbance, and its safety throughout pregnancy is not yet established. On the other hand, inositol is a nutritional supplementation, its intake is not associated with any significant side effects, and its co-administration with gonadotropin resulted in less vigorous ovarian response and the consequent decrease in cancellation rate and improved PR.

INOSITOL AND PREGNANCY

When a woman with PCOS gets pregnant, she is more likely to develop GDM. Should we stop Inositol now that she is pregnant?

Inositol is an important nutrient required throughout pregnancy. The fetus, gets its inositol from maternal blood. Studies have shown that in mid-gestation, the MI concentration in venous blood from the umbilical cord was fivefold higher than that detected in the maternal serum. At term, serum MI concentration of the neonates decreased, but it was still two- to threefold higher than in maternal blood

During pregnancy, women experience an increase in oxidative stress and some pregnancy disorders are associated with both high levels of oxidative stress and unbalanced levels of some micronutrients in the maternal blood. MI seems to restore and maintain a healthy pregnancy and fetal development. MI promotes the differentiation of the fetal lung and prevents neural tube defects. The uptake of MI from embryonic cells is competitively inhibited by glucose. It has been suggested that congenital malformations, especially of CNS and heart, observed with high frequency in infants born to diabetic mothers could be attributed to hyperglycemia induced tissue specific shortage of MI15.

Several studies have reported that folate resistant neural tube defects could be prevented by combining MI with folic acid.

INOSITOL, DOSAGE

The levels of MI and DCI in different tissues in the body was studied and it was observed that a specific MI/DCI ratio exists within each tissue. It was also noted that the plasma ratio of MI to DCI in healthy subjects was 40:1. High DCI levels (even if always lower than MI concentration) are generally observed in glycogen storing tissues (fat, liver, muscle), whereas low DCI

levels are present in tissues characterized by high consumption of glucose (brain, heart, ovaries).

The therapeutic range of MI in PCOS is 2 to 4 grams. Pharmaceutical products are now available with this dosage and ratio 40:1. This innovative formulation is particularly useful in the management of PCOS because of its,

(1) action on liver, mainly exerted by DCI, aimed at reducing insulin levels

(2) selective effect on the ovary, where MI is thought to counteract the increased DCI levels, and hence reestablishing FSH sensitivity.

Duration of treatment is 3 months to one year and the action is seen within three months. Caffeine reduces the action of MI.

SAFETY OF INOSITOL

Commonly used dosage of Inositol in clinics is 4g/day. This is completely free of side effects. Human clinical trial data indicate that adverse events related to MI treatment are: Gastrointestinal symptoms (nausea, flatus, loose stools, diarrhoea) at dose of 12 g/day or higher. Furthermore the severity of adverse events stays the same also at 30 g/day.

COCHRANE REVIEW

Evidence from four trials of antenatal dietary supplementation with myo-inositol during pregnancy shows a potential benefit for reducing the incidence of gestational diabetes. However, the current evidence is based on small trials that are not powered to detect differences in outcomes including perinatal mortality and serious infant morbidity. All of the included studies were conducted in Italy which raises concerns about the lack of generalisability of the evidence to other settings16. Further trials for this promising antenatal intervention for preventing GDM are encouraged and should include pregnant women of different ethnicities and varying risk factors and use of myo-inositol (different doses, frequency and timing of administration) in comparison with placebo, diet and exercise or pharmacological interventions.

CONCLUSION

Clinical data have shown that Inositols, particularly MI and DCI are found to be effective in the management of Insulin resistance in women with PCOS and improving the quality of Oocytes in IVF(Level 1a evidence17). Supplementation of Inositol has also been useful in the management of hyperandogenemia (acne and hirsutism), regularizing menstrual cycles and in improving fertility in women with PCOS. Continuing Inositol in pregnancy can avert the development of Gestational Diabetes. The beneficial effect extends to alleviating the metabolic problems in women with PCOS. More RCTs are required to strengthen the evidence for the use of Inositol in PCOS, in preventing GDM and in preventing metabolic disturbances.

KEY POINTS

- Inositol is a carbohydrate normally present in the body. It works as a second messenger for various cell processes.
- MI and DCI are two important isomers of Inositol.
- Both MI and DCI are involved in the process of insulin signalling, displaying different actions.
- DCI reduces hyperinsulinemia and increases glycogen synthesis.
- MI displaces the intrafollicular DCI in excess, allowing the signal amplification of FSH and glucose reuptake.
- Their combined treatment in the physiological ratio 40:1 is an effective strategy targeting metabolic needs as well as endocrine requirements in women with PCOS BMI>25.
- At the ovarian level treatment with MI improves oocyte and embryo quality as well as the ovarian response to FSH

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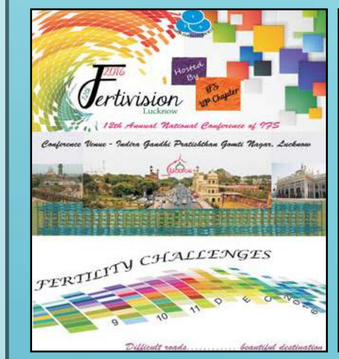

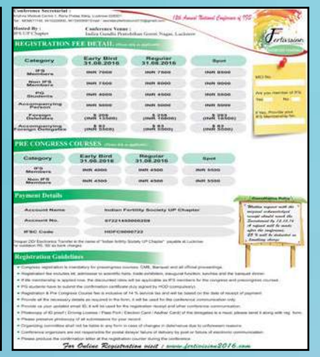

ESHRE CORNER

Paper Presentation in 32nd ESHRE Conference at Helsinki, Finland, from 3rd to 6th July, 2016.

Dr. N.C. Chimote
Dr. Bindu Chimote
Dr. Amogh Chimote
Dr. Nishad Chimote
Dr. Randhir Singh
Dr. Monica Singh
Dr. Umesh Jindal
Dr. Puneet Rana Arora

ESHRE EMBROYOLOGY CERTIFICATION

Cracking ESHRE Embroyology Exam in July, 2016	
Dr. Praney Ghosh	Delhi
Dr. Gaurav Kant	Delhi
Dr. Sanjiv Kumar Maheshwari	Chandigarh
Our Previous Successful IFS Members in June, 2014	
Dr. Randhir Singh	Bhopal
Dr. Yogesh Khanna	Varanasi
Dr. Sarabhjeet Singh	Delhi

IFS ACTIVITIES UNFOLDING

SPECIAL INTEREST GROUPS - PLAN FOR THE YEAR 2016-18

It has been decided to form 12 Special Interest Groups which has been created for a period of 2 years (2016-2018) for a more focused interaction among the IFS members. More SIGs will be formed in future as per requirement.

Each SIG is lead by eminent specialists and they are required to conduct 2 CMEs every year for the benefit of other IFS members. All activities of the SIG should be with prior approval of IFS Secretariat.

IFS Members who are keen to join any SIG may please email their short CV to IFS Secretariat, clearly mentioning the name of group they want to join.

The various Special Interest Groups and their Convenors and Co- Convenors at present are as follows:

Chair : Dr. Sohani Verma (President IFS)
Co- Chair : Dr K.D. Nayar (Secretary General IFS)

S.No	Special Interest Groups	Convenor	Co- Convenor
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CHAPTER ACTIVITIES

BIHAR CHAPTER

CME held at Patna on 17-6-2016




PUNJAB CHAPTER

CME held at Patiala on 24-4-2016





ACTIVITIES AT DELHI

Two International Video conferences (VC) held in April 2016


MID TERM MEETING

at Delhi 20-21 Aug




JAMMU CHAPTER

CME held at Jammu on 7-08-2016

GR. CHANDIGARH CHAPTER

CME on Fertility & ART on 11-9-2016





UP CHAPTER

PREPARING TO HOST FERTIVISION 2016 AT LUCKNOW

CME held at Lucknow on 21-5-2016






CME held at Kanpur on 19-6-2016

CME held at jounpur on 6-7-2016

CME held at Lucknow on 2-8-2016

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