ISSUE 1 | Pages 16 | June 2017

www.isarindia.net

A Newsletter of the Indian Society for Assisted Reproduction

isar Express

Indian Society for Assisted Reproduction

2017-2018 – ISAR's year of **E**ducation, **E**thics, **E**mpathy

ISAR Office: Flat No. 23-A, 2nd Floor, Elco Arcade, Hill Road, Bandra (W), Mumbai 400050.
Tel. 26456488 , 26406070, email: isar.office@gmail.com

ISAR Executive Committee 2017-2018

Dr. Duru Shah
President
durushah@gmail.com
isarpresident@gmail.com

Dr. Ameet Patki
Hon. Secretary General
aspaap@hotmail.com

Dr. Mahendra N. Parikh
Founder President

Dr. Narendra Malhotra
Immediate Past President

Dr. Rishma Pai
President Elect

Dr. Jaideep Malhotra
Vice President

Dr. Prakash Trivedi
Second Vice President

Mr. Virendra Shah
Chairman, Embryology

Dr. Sudesh Kamat
Vice Chairman, Embryology

Dr. A Suresh Kumar
Hon. Joint Secretary

Dr. S Krishna Kumar
Hon. Treasurer

Dr. Sunita Tandulwadkar
Hon. Joint Treasurer

Dr. Sujata Kar
Hon. Clinical Secretary

Dr. Asha Baxi
Librarian

Dr. Madhuri Patil
Editor of JHRS

Past Presidents

Late Dr. Mehroo Hansotia

Dr. Firuza Parikh

Dr. Kamini Rao

Dr. Sadhana Desai

Dr. Manish Banker

Dr. Dhiraj Gada

Dr. Hrishikesh Pai

Members

Dr. Bina Vasan

Dr. Charudutt Joshi

Dr. Himanshu Patel

Dr. Kedar Ganla

Dr. Laxmi Shrikhande

Dr. M S Srinivas

Dr. Milind Shah

Dr. Parul Kotdawala

Dr. R B Agrawal

Dr. Rajat K Ray

Dr. Rajesh Modi

Dr. Sanjay Makwana

Co-opted Members

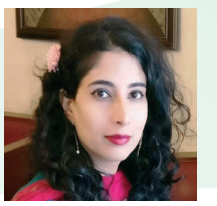
Dr. Gautam Khastgir

Dr. Kanti Bansal

Dr. Nimish Shelat

Dr. Padma Rekha Jirge

Co-Editor, ISAR Express



Dr. Sabahat Rasool

President's Message

Dr. Duru Shah
President, ISAR

Chief Guest, Dr. Christos Coutifaris, President Elect American Society of Reproductive Medicine. Guest of Honour Dr. Rishma Pai, President Federation of Obstetric and Gynecological Societies of India, immediate past president Dr. Narendra Malhotra, immediate past honorary secretary Dr. Prakash Trivedi, organizing chair persons of this conference Dr. Poonam Loomba and Dr. Maninder Ahuja, dignatories on the dais and in the audience, past presidents of ISAR, my colleagues in ISAR, members of the Industry, members of the media, my friends, and my husband, Dr. Sushil Shah.

I congratulate Dr. Narendra Malhotra, Prakash Trivedi and team for a marvellous program through the last 14 months and Dr. Maninder Ahuja, Dr. Poonam Loomba and their teams, for having organized this brilliant meeting which I am sure all of us will truly enjoy!

It is my privilege to take charge as President of the Indian Society of Assisted Reproduction, and I accept this honor with humility. I affirm that I, along with the honorary secretary of ISAR, Dr. Ameet Patki and my team, will do our best to further strengthen this very prestigious professional Organization of experts in the field of Infertility.

India has a strange problem. On the one hand it has the burden of high fertility which the Govt. is handling effectively through various family planning programs, and on the other hand we have the problem of infertility, with about 15 % of currently married women being infertile with serious demographic, social and health implications.

The Global Journal of Medicine and Public Health has reported that infertiltiy leads to increased maternal and reproductive health problems, increases violence against women with significantly higher divorces among infertile women than those who have proved their fertility.

The study has also very elegantly shown that the differences in childlessness depends on whether they live in urban cites or villages, their religion, caste and tribe, and their socio- economic and educational status. Infertile women also face immense emotional and psychological trauma, as culturally, infertility is a social stigma in our country.

Infertility is a huge social problem for women in India, whether the infertility is due to causes within a woman or her husband, it is she who is targeted, she is the one who has to visit her gynecologist and reveal her most private information, not once, but multiple times to different people in the clinic, she is the one who is answerable to everyone asking her "When are you planning to be pregnant?"

If assisted reproduction such as IVF is required by a couple in rural India, the couple may have to stay away from their homes in order to manage the frequent visits to infertility clinics which are far away from their homes. Hence the entire cost of treatment goes up tremendously, which includes the cost of medical treatment, cost of travel including stay to the city of treatment, with the added loss of income due to absenteeism from work. In order to avoid this loss to them, ISAR needs to reach out to them rather than them travelling to seek fertility providers. Hence it is necessary for us to encourage and train healthcare providers to ensure the highest standards of care.

On the other hand, in the urban areas, especially in the lower socio-economic group, whilst couples undergo treatment, women may have to take leave from their jobs, or take some time off from their careers in order to reach the clinics, as and when required, only because biologically it is they who get pregnant. Besides not many can afford the costs involved and if they are desperate to get pregnant, with a possibility of affording only 1 cycle of IVF, they may agree to any kind of unindicated treatment such as egg donation, sperm donation embryo donation, only because they are under extreme pressure to get pregnant. We need to have better monitoring, vigilance and surveillance to ensure safety standards for women across India. This will help IVF Centers to function with the best standard of care and practices.

As an Indian I feel very proud that ISAR has advanced so well the field of Assisted Reproduction. We have made huge strides in reaching out to women but we need to ensure that our field maintains a high level of a professionalism and accountability by reporting to our Registry NARI, which will help us to offer Indian data and be part of the Global arena.

As an exceedingly concerned Indian first and a doctor later, I feel it is important to address these issues. As President of ISAR, I would like to dedicate 2017 as "**ISAR's year of Empowerment: through Education, Ethics and Empathy**".

My mission will be to bring this agenda center stage by raising awareness on it and advocating for women's reproductive rights, which include access to treatment for infertility.

I understand that the nation needs to focus on controlling our population and reduce maternal mortality, but in the process we cannot neglect the problem of infertility! Because when we treat infertility, women get pregnant and have a healthy start. Both these areas go hand in hand and are integrated. Our field makes women pregnant, and we need to ensure that multiple pregnancies are prevented and we should contribute to healthy pregnancies. We need to help to reduce maternal mortality, and morbidity, such as secondary infertility, which results from an infected delivery or abortion.

I have this agenda uppermost in my mind and it is through ISAR, that we will exchange our views with the Government on how we can take this agenda further. Every woman and man has the right to attempt a pregnancy, and IVF has given millions of couples a child of their own, and we need to respect their rights.

There is an urgent need to include coverage for infertility services for women who are covered by health insurance, so that they can take a break from their jobs in order to undergo such treatments. This will prevent them from facing a double financial loss, of paying for their treatment and losing the financial support of their jobs. The Insurance Sector needs to be motivated to cover costs related to infertility treatments as is seen in many western countries. Similarly we need to assist rural women by offering safe infertility services through public private partnerships with infertility clinics, which are accredited by a Professional Organization, such as the Indian Society of Assisted Reproduction (ISAR).

Newer technologies are developing very rapidly in the field of ART, and as IVF specialists we need to be constantly updated, so that we can offer the best of care to our women.

Let us act by practicing evidenced based medicine and not get swayed to be the first in offering a technology, which may not really be the best for our women, men and their future children. Let us be ethical in our practices, for the good of our patients and for the good of our population. We in India need to be self-regulated, because we are not monitored by agencies such as HFEA in the UK. Till such agencies are in place, we must remember, that we are being monitored by someone more supreme up there!

As infertility treatments are very basic in Government and Municipal hospitals where most of our budding doctors train and become gynecologists, they only learn this science theoretically and have very limited practical experience on managing infertility with assisted reproduction. Education is one of our agendas this year and ISAR will take up this challenge through this year.

Continued on page 4

State Chapters

Bihar Chapter
Dr. Shanti Roy, Chairperson
Dr. Pragya Mishra, Secretary

Chhattisgarh Chapter
Dr. A. Suresh Kumar, Chairperson
Dr. Tripti Nagaria, Secretary

Delhi Chapter
Dr. G K Tripathi, Chairperson
Dr. Shivani Sachdev Gaur, Secretary

Gujarat Chapter
Dr. Kanthi Bansal, Chairperson
Dr. R G Patel, Secretary

Haryana Chapter
Dr. Maninder Ahuja, Chairperson
Dr. Jyoti Malik, Secretary

Karnataka Chapter
Dr. M S Srinivas, Chairperson
Dr. Shobhana Patted, Secretary

Kerala Chapter
Dr. Sathy M Pillai, Chairperson
Dr. Fessy Louis, Secretary

Maharashtra Chapter
Dr. Nandita Palshetkar, Chairperson
Dr. Padmarekha Jirge, Secretary

MP Chapter
Mr. Virendra Shah, Chairperson
Dr. Gajendra Tomar, Secretary

North East Chapter
Dr. Arun Madhab Baruah, Chairperson
Dr. Vijay Nahata, Secretary

Orissa Chapter
Dr. Jayshri Pattnaik, Chairperson
Dr. Babita Panda, Secretary

Punjab Chapter
Dr. Virk Surendra Pal Singh, Chairperson
Dr. Surjit Kaur, Secretary

Rajasthan Chapter
Dr. M L Sawarankar, Chairperson
Dr. Renu Makwana, Secretary

Tamilnadu & Pondicherry Chapter
Dr. Kamala Selvaraj, Chairperson
Dr. Sanjeev N Reddy, Secretary

Telangana Chapter
Dr. Mamata Deendayal, Chairperson
Dr. Shantha Kumari, Secretary

UP Chapter
Dr. Jaideep Malhotra, Chairperson
Dr. Anupam Gupta, Secretary

West Bengal Chapter
Dr. Gita Ganguly, Chairperson
Dr. Gautam Khastgir, Secretary

President's Message *Continued from page 3*

ISAR FLAG

There is a need to offer good postgraduate courses to them including fellowships and mentorships with experienced clinics, for them to learn this art. ISAR is the body which Is doing its best to offer such training which is gradually getting very popular and during my tenure I will be initiating many more such programs.

ISAR is a mature Organization which needs its own identity. I would like to launch the new **ISAR Logo** which stands for "**Integration of various disciplines towards one common goal of making an infertile woman pregnant**" and our own "**ISAR Flag**"

ISAR LOGO

I would like to quote my favorite hero "**Mahatma Gandhi**" who said "**You may never know the results of your actions, but if you do nothing, there will be no results**". Keeping his spirit in mind, let's act, today!

I would like to end by thanking all those who have walked with me through my journey and will continue to walk with me. I thank all of you for being here to share my thoughts and the responsibilities we have towards our women. I am sure all of you who have affirmed your confidence in our team will support us, because without your support, we will not be able to deliver. Our team at ISAR will work hard for all of you and make sure that all of you get what you aspire from ISAR.

I would also like to thank

- all my colleagues who will take our agenda forward through the year.
- all our industry partners for supporting our initiatives through the year.
- my team at Gynaecworld
- and my family members who have always encouraged me to do even better.

Dr. Duru Shah
President, ISAR

Hon. Secretary's Message

Dr. Ameet Patki
Hon. Secretary, ISAR

Dear Colleagues

It is my pleasure and honor to write for the first issue of ISAR Express for the year 2017-18. This issue is released under the guidance of our President Dr. Duru Shah who with her expertise and finesse will raise the standards of our organization.

This year we intend to roll out new, practice oriented and evidence based educational modules to keep ourselves abreast of all new developments in our specialty. Science and technological innovations are happenings at a fast pace and ISAR Express is one of the ways that we intend to keep our members informed of the latest in the world of reproductive medicine.

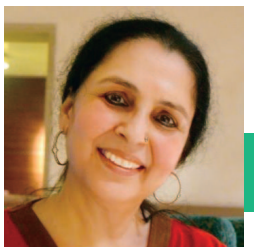
ISAR as an organization is equally committed and responsible towards the patients we treat and care for. The responsibility of reproductive freedom. This is critical to a whole range of issues that we deal with in our daily practice. Reproductive freedom should not be seen as a privilege or as a benefit but as a fundamental right of all those interested in procreating. ISAR will strive to work towards it.

I hope you enjoy this issue as much as the editorial board enjoyed bringing it out for you.

Regards

Ameet Patki
Hon Sec. General ISAR

22nd Annual Congress of ISAR – Hyatt Regency Gurugram



Dr. Poonam Loomba
Organizing Chairperson

The 22nd annual congress of ISAR, 2017 was organised by the Haryana State Chapter under the leadership of President ISAR 2016-2017, Dr. Narendra Malhotra, with Organising Chairperson, Dr. Poonam Loomba, Host Chairperson, Dr. Maninder Ahuja and Secretary, Dr. Jyoti Gupta.

Dr. B. N. Chakraborthy being presented his potrait

Dr. Sadhana Desai being presented her potrait

This was so far the largest congress in terms of number of delegates, faculty, academics and workshops in the field of Assisted Reproductive Technology. The Congress was designed around its theme of Illuminating Fertility Treatments: Basics and Beyond. The scientific committee developed exhaustive scientific sessions which included many panels ,debates, and industry sponsored sessions from Merck Serono, Ferring and MSD. ASRM session was supported by speakers, Dr. Richard Reindoller, CEO ASRM, Dr. Christos Courtifaris (President elect ASRM).

There was a three day training module by ASRM on Embryo transfer simulators and many delegates took special training from Dr. Richard Reindoller, Dr. Christos Courtifaris and Mr. Keith Ray.

Installation of the New President, Dr. Duru Shah

For the first time there was participation from ESHRE in ISAR with efforts made by Dr. Poonam Loomba and Dr. Narendra Malhotra. ESHRE session was supported by Dr. Nazar Amso from Cardiff-London and Dr. Zdravka Velvea from Finland. Both the speakers applauded ISAR and the hospitality extended to them from ISAR, 2017 and expressed their desire to continue this association.

There was a special ISAR- ASPIRE PG Refresher course, jointly organised by Dr. Duru Shah and Dr. Jaideep Malhotra from ISAR and Prof CR Tzeng and Dr. Jung Ryeol Lee from ASPIRE. It was attended by over 100 students. The Aspire session was supported again by Dr. Jung Ryeol Lee and Prof CR Tzeng.

Book Release

The FIGO session was supported by Dr. David Adamson from USA.

More than 25 International guest speakers were invited from USA, Australia, Japan, United Kingdom, Middle East and Bangladesh.

Dr. Narendra Malhotra delivered a key note address on Innovations in ART. Dr. Duru Shah, President ISAR 2017-18, discussed 'The End of Sex and the Future of Human Reproduction' in her plenary Oration. Dr. Richard Reindoller as an invited international guest speaker covered Unexplained Infertility in his oration.

As an overview of ISAR 2017, undoubtedly this has been one of the best congresses in terms of academics, hospitality and team effort. We can proudly say that the international standards of organising any academic event were maintained. This was a dream project of Haryana chapter made true by cooperation of all senior executive members of ISAR, all members of ISAR and all members of Haryana chapter.

Dr. Pratap Kumar receiving Dr. Duru Shah Life Time Achievement award

Dr. Firoza Parikh receiving Dr. Prabha Malhotra Memorial Life Time Achievement award

Dr. Vijay Mangoli receiving Dr. Gautam Khastagir Life Time Achievement award

The Lotus Study – An International Multicentric Trial

"Oral dydrogesterone (DYD) is non-inferior to Micronized Vaginal Progesterone (MVP) for luteal support in in vitro fertilization (IVF)".

Reference

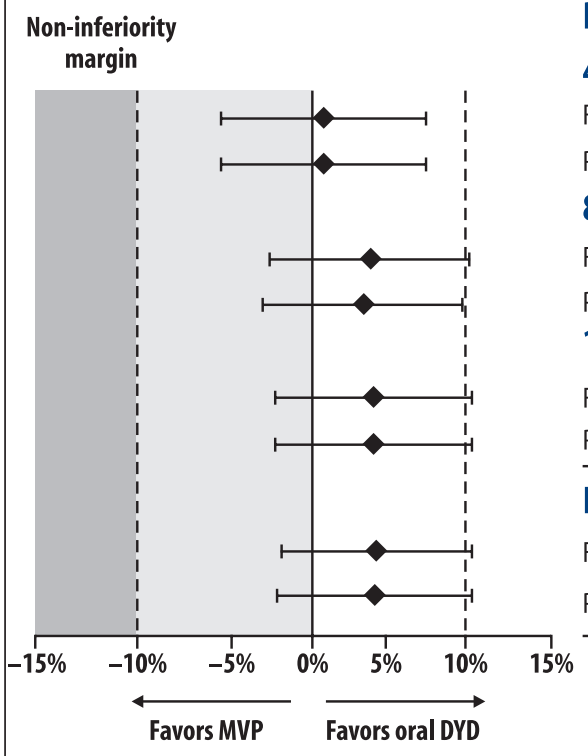
Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. Hum Reprod. 2017 May 1;32(5):1019-1027. doi: 10.1093/humrep/dex023.

MVP is being extensively used for luteal phase support in IVF. Vaginal discharge and irritation are the most common side effects which affect patient acceptance and tolerability. Recently, a phase III double-blind double-dummy multicenter randomized controlled trial, Lotus I, across 38 sites in Austria, Belgium, Germany, Finland, Israel, Russia and Spain between 2013 and 2016 was carried out. 1031 patients were randomized to receive either oral dydrogesterone 10 mg thrice daily or MVP 200 mg thrice daily from the day of oocyte retrieval until 12 weeks of gestation, if a positive pregnancy was obtained 2 weeks after embryo transfer.

The primary objective of the study was to demonstrate non-inferiority of oral dydrogesterone versus MVP by assessing fetal heartbeat at 12 weeks of gestation. Secondary objectives included positive pregnancy test at treatment day 15 after embryo transfer & incidence of live births. The primary efficacy analysis used a two-sided 95% confidence interval (CI) with a non-inferiority margin of 10% for the difference in pregnancy rates between dydrogesterone and MVP, whereby the former was found to be non- inferior to MVP.

The number of embryos transferred was similar between the two treatment groups. Pregnancy loss after 8 weeks of gestation, which included spontaneous abortions, induced abortion due to illness of the fetus and loss to follow-up, was similar between groups, with rates of 5.0% and 5.6% being observed in the dydrogesterone and MVP groups, respectively. Additionally, dydrogesterone was well-tolerated. The proportion of patients reporting treatment-emergent adverse events (TEAEs) was 56% in dydrogesterone group and 54% in the MVP group. The proportion of serious TEAEs was similar between the two groups. Infant safety data at delivery was similar between the two groups.

The Lotus I Study concluded that oral dydrogesterone was non inferior to MVP for fetal cardiac activity at 12 weeks and pregnancy and live birth rates in IVF, and has a similar safety profile to MVP. Taking into account the safety data collected in this study, dydrogesterone exhibited a favorable benefit/risk profile. The results of this study have the potential to induce a paradigm shift for the treatment of the estimated 1.5 million women worldwide undergoing IVF each year.



Outcome	% (n/N) Oral DYD	% (n/N) MVP	Difference in pregnancy rate (Oral DYD–MVP)	95% CI
Pregnancy rate				
4 Weeks of gestation				
FAS	47.1 (234/497)	45.5 (217/477)	1.7	–4.4 –7.9
PPS	47.2 (232/492)	45.5 (216/475)	1.8	–4.4 –8.0
8 weeks of gestation				
FAS	39.6 (197/497)	35.4 (169/477)	4.3	–1.7 –10.3
PPS	39.6 (195/492)	35.6 (169/475)	4.1	–1.9 –10.1
12 weeks of gestation				
FAS	37.6 (187/497)	33.1 (158/477)	4.7	–1.2 –10.6
PPS	37.6 (185/497)	33.1 (157/475)	4.7	–1.2 –10.6
Live birth rate				
FAS	34.6 (172/497)	29.8 (142/477)	4.9	–0.8 –10.7
PPS	34.6 (170/492)	29.9(142/475)	4.7	–1.1 –10.5

A short commentary by Dr. Duru Shah & Dr. Sabahat Rasool

"Women undergoing Assisted Reproduction need to have an efficient Luteal Support. This has been offered by fertility experts in the form of daily injections of Progesterone which can be very painful, or as vaginal micronized progesterone which can cause vaginal irritation rashes and discharge . The results of this study, will definitely encourage us to try the oral route which may be more convenient and less trouble to women."

ASRM Showcases Its Embryo Transfer Simulator at ISAR

Dr. Richard Reindollar
ASRM Ceo

Dr. Christos Coutifaris
ASRM President Elect

The American Society for Reproductive Medicine (ASRM) hosted a Post-Conference Workshop on embryo transfer protocol and hands-on simulation. "The ASRM was honored to be invited to participate and host a workshop during the 2017 Indian Society for Assisted Reproduction (ISAR) Annual Meeting in Gurgaon", stated Dr. Richard Reindollar (ASRM CEO). Preceding the ASRM's Workshop on Embryo Transfer using simulation, the ASRM Embryo Transfer Simulators were also made available for conference attendees to participate in "brief" training sessions on Conference days 1 & 2. Drs. Richard Reindollar and Christos Coutifaris (ASRM President Elect) provided expert guidance in embryo transfer techniques to over 150 participants during the conference.

"For both patient and physician, the final step of IVF - the transfer of the embryo into the uterine cavity for implantation - is the most crucial step and often the most stressful step", states Dr. Coutifaris, stating further "that this anxiety is often attributed to the high cost and time associated with IVF/ART and the potential difficulty of the transfer due to individual patient anatomy." The ASRM Embryo Transfer Simulator is a robust training simulator that provides physicians and healthcare workers the opportunity to practice simulated transfers and intrauterine insemination using a variety of challenging uteri. It requires the learner to attain the skills needed to successfully navigate normal and difficult endocervices using either ultrasound-guided or un-guided imaging to simulate placing the embryo(s) in the ideal location within the uterine cavity. "It is always amazing to see the high level of enthusiasm and the focused determination the participant demonstrates while trying to navigate the different, challenging endocervical canals. It also equally rewarding for the learner and the simulation proctor when the correct adjustment(s) are made to learner's technique which allows the catheter to reach the internal os, at which point the learner is then able to identify and achieve ideal placement of the embryo", says Dr. Reindollar.

Simulation-based training allows for training in a safe, risk-free environment and the ability for unlimited repetitions and deliberate practice methods. "Nearly 50% of in-training physicians in the U.S. have historically received little or no training in embryo transfer because of the importance of this final step in the IVF process and the difficulty in allowing trainees to perform it on patients for the first time," Dr. Reindollar explains. Participants in the ASRM simulation sessions received real-time simulation metrics (feedback) and structured debriefing with the expert faculty, two key areas of simulation that help facilitate development of motor and cognitive skills required to attain proficiency in embryo transfer. In conjunction with the ASRM Curriculum for Embryo Transfer and the ASRM Standard Embryo Transfer Protocol, the Simulator is a tool that significantly augments current physician training using a structured simulation-based method to learning basic embryo transfer techniques and characteristics of an ideal transfer.

Assessing the Quality of Ovarian Stimulation

Zdravka Veleva
MD, PhD
Helsinki University and Helsinki University Central Hospital, Finland

The aim of ovarian stimulation for IVF/ICSI is to ensure the simultaneaous growth of several follicles containing good quality oocytes. Ovarian stimulation protocols were taken into use in the 1980s, first with fixed and later with flexible daily gonadotropin doses. The 1990s saw the development of the long, short and ultrashort gonadotropin-releasing hormone (GnRH) agonist protocols. GnRH antagonist protocols were also introduced. During the 2000s, discussion shifted towards the mild GnRH agonist protocol, in which relatively smaller gonadotropin doses were used. Lately, protocols have evolved to include luteal-phase stimulation as well.

Even though they can be used in many cases, each protocol has its specific target group of patients. For example, GnRH antagonist is recommended when the patient is at risk of ovarian hyperstimulation syndrome while luteal-phase stimulation might be more suitable for women with diminished ovarian reserve. However, during the last few years there has been a call for reconsidering the principles of ovarian stimulation even in patients with good prognosis in order to ensure good quality of stimulation.

The quality of ovarian stimulation relates to creating the best embryos and endometrium for each specific case that will lead to complication-free pregnancy and the birth of at least one healthy child. The quality is affected by female infertility factors such as age, obesity, infertility diagnosis and ovarian reserve. What makes the assessment of ovarian stimulation quality difficult is the fact that it cannot be measured directly. Oocyte quality cannot be reliably examined whereas blastomere biopsy is expensive, time-consuming and not 100% effective. Furthermore, biopsy of the endometrium before transfer is not possible and there are no reliable ways of assessing its receptivity even nowadays.

There is currently no consensus on how to evaluate the quality of ovarian stimulation. However, the ongoing debate on ovarian stimulation between European and U.S. practitioners reveals the most important factors of stimulation quality. According to the European view, oocyte quality is better with relatively lower gonadotropin doses, whereas in the U.S., accent is placed on the high number of oocytes retrieved regardless of gonadotropin dose. Lately, U.S. strategy has been re-evaluated as a study in 2015 revealed low live birth rates with very high gonadotropin doses.

This debate reveals that the two most essential components of ovarian stimulation are gonadotropin dose and the number of oocytes retrieved. Research from Finland has shown that the relationship between gonadotropin dose and number of oocytes retrieved is useful in assessing stimulation quality as it correlates with cumulative live birth rates. Even in cases with high oocyte numbers, if total gonadotropin dose per oocyte retrieved is high, outcome is worse, compared with cases with low gonadotropin dose per oocyte retrieved. Clinicians can use this relationship as a new easy-to-use tool to optimize starting gonadotropin doses in a subsequent stimulation.

Debate

Prof. Sadhana Desai
MD, FRCOG
Past President, ISAR.
Senior IVF Expert

1. First of all, the term "commercial surrogacy" is not correct. Let it be considered as "Compensated surrogacy", and I am very much in favor of it. Do you think in current era of nuclear family, all couples with the medical need of having a baby with surrogacy will be able to find a female in the family to be ready for giving 10 to 12 months of her life without in turn being benefited? It is not possible in 99%. The open arrangement for compensation is much better and efficient. And what is wrong if the needy women get benefited by this noble arrangement. Why do people think that surrogates are doing surrogacy just for money and consider it commercialization and commodification? Surrogates themselves have different noble motive of pursuing the practice. They do it for the education of their children, construction of a house, treatment of a family member and so on. They don't do it for money for luxury. Commercial surrogacy brings happiness in two families without chances of conflicts in future. It is a win-win situation for both the parties.
2. Kiran Rao had multiple miscarriages and Gauri khan being 45 years, who said there were no medical indications? Tusharkappor and Karan Johar are single fathers. To have a baby or not and by what mean shall be a personal choice. Media has wrongly overrated these cases It is not the surrogacy but the hype created by media which has given this issue a wrong angle. Era of social networking and over access to internet has made people critics & judges who easily poke in lives of others.
3. No. It depends on the wish of intended parents and surrogates both. Baby feeds on her/his biological mother's milk if she has opted for induced lactation or else surrogate's milk is given to the baby.
4. What is this? This question itself is completely wrong. Why people think this way? Don't you feel, people in the haste of showing more affection towards surrogates, completely ignore the pain, love and feeling of the real mother who had had undergone numerous IVF failure or any traumatic medical procedure to have this baby. In fact the baby is lucky to get two mothers and love from 2 families.
5. There is always way out for every problem. Government should make regulations for compensated surrogacy and should not ban it. Otherwise there will be unhappy childless marriages, divorces, suicides, depressions.
6. "Renting womb" is the term given by media. Surrogate never rents her womb, she donates her womb for nine months. She gifts motherhood to one unfortunate woman who herself can't carry her baby for nine months. It's a noble cause and surrogates themselves feel its importance.
7. Yes. Media and all people, who are blessed with fertility, should understand the difficulty of infertile couples and stop being negative unnecessarily for this practice.

Prof. Gamal I. Serour
MD, FRCS, FRCOG
Past President, FIGO. Director of the International Islamic Center for Population Studies and Research, Al Azhar University, Clinical Director of The Egyptian IVF & ET Center, Egypt

1. It involves exploitation of human beings and their bodies, involves coercion of the needy and the poor. Therefore if it is done, it should be very tightly regulated.
2. Indeed Yes. Motherhood is a gift which should be achieved either through natural or assisted conception, when needed, based on medical indications. It is not a commodity to be bought from the underprivileged women.
3. It does not, if arrangements are made with the surrogate mother to breast-feed the child. This has been practiced in various cultures for thousands of years and such women are known as lactating mothers.
4. Certainly it is unjust, as much as it is unjust to deprive the baby inside the womb from the care and protection of his/her genetic mother who would be keen to provide to be born with every possible protection.
5. It should be clear in our mind that pregnancy and childbirth are not an industry even if they can generate a source of income for individuals, societies, or countries. Those couples who can afford surrogacy to have a baby should seek alternatives as uterine transplant or adoption. The state should provide funds to support and educate the poor and the needy rather than coercing them to turn their bodies to commodities for renting or sale.
6. Surrogacy is not like organ donation. It involves a third party, who is the child to be born, and its rights should be considered in the equation.
7. Certainly Yes. The gift of life and altruism should be protected from malpractices and irregularities which jeopardize this noble objective of continuation of human life on earth.

From An Ever-Grateful Father who has Used the Services of a Surrogate

1. The surrogate mother of my child was a lady I will never forget. After delivering our beautiful, healthy little baby we were lucky enough to meet. Her maternal demeanor permeated the room and her emotional attachment was towards both us and the newborn baby. Our surrogate who was carefully screened and selected by our ART Clinic was committed to giving a part of herself in order to give someone less fortunate a child and the happiness that comes with it.

   The remuneration was no more than a practical necessity.
2. As a non-resident of India I cannot comment about the perception the public has towards "celebrity babies". If this is about real life celebrities who prefer

Half Truths & Untruths about Surr

Dr. Sabahat Rasool
MD, DNB, MNAMS, FMAS, MRCOG (UK).
Ian Donald Diplomate in OBGYN Ultrasound.
Fertility Consultant,
Gynaecworld Fertility Center

Surrogacy is an alternate way to form a family a
legalization of commercial surrogacy in 2002, Ind
cost efficient medical care, excellent ART facilities a
resulted in a boom and the 15 year-old industry
mushrooming IVF industry with no clear-cut gui
path to a surrogacy ban bill being in the pipeline.
but even the guidelines laid down by the Indian co
by the majority of this reprotech industry. With th
Gestational or commercial surrogacy, alternately
means to assist those desperate couples who canno
of this arrangement still haunts its opponents.

Gestational surrogacy should be a part of compreh
centers, with a full back up of lawyers, counselor
seriously consider enacting a law to regulate surrog
the surrogate, the child born through surrogac
preventing exploitation of any of them.

Questions

1. Criticized by the right groups on one hand, an only & final chance to make a one-time fina could never dream of by renting their wombs
2. Has surrogacy, which is not medically indicate a wrong angle?
3. Does surrogacy completely deny a child his/h
4. Is it just to separate a just-born baby from the In other words does the baby get half-orphan
5. After the ban in India, there will be couples w baby. These include those with absent/hypop for some medical reason, cannot fathom to bea for a baby and those desperate for funds to su path with appropriate laws and safeguards to
6. Some surrogates pose the question as to why
7. Over 99% of surrogate mothers willingly relinq up in a legal tiff to claim the child. The med which further reinforces the bad image of co the vast majority who has been blessed with gift of life and altruism instead?

We conducted a panel discussion. Here are the speakers.

ogacy – from all Stake holders

nd dates back to Biblical & prehistoric times. With ia became the Surrogacy capital of the world. Low nd easy availability of needy commercial surrogates was already generating 2.3 billion USD in 2012. A delines or legislation in place has final paved the . Agreed, there were no stringent laws and checks, uncil of Medical Research, ICMR, were not followed e result, a complete surrogacy ban is on the cards. hailed and criticized by one and all, is an excellent ot bear a child. Nevertheless, the commercial nature

hensive infertility treatment program in accredited rs and ethics committee. The government should acy in India in order to protect the intended parents, cy, and the Assisted Reproduction Centers, thus

d embraced openly by many needy women as the ncial package which as uneducated women they s. What is your take on commercial surrogacy?

ed, such as celebrity babies in India given this issue

er right to breastfeed?

womb that nurtured it through the nine months? ned?

ho will be left with absolutely no choice to have a plastic or abnormal uterus and those women who, ar a pregnancy. Are we being fair to those desperate pport and educate their children? Is there a middle streamline a 'rouge industry'?

we equate surrogacy with organ donation?

quish the child and it is less than even 1% that ends ia hype, however, focuses on the negative issues, ommercial surrogacy. We very conveniently forget a child through surrogacy. Could we focus on the

the Answers to the questions by each of

to use a surrogate in order to preserve their career then it does indeed raise ethical concerns. Will the celebrity love their child as much knowing they "rented a womb" rather than put their own livelihood at risk? Is it fair to use a surrogate to do this? It is important to remember that if done properly as has been my experience the surrogate is not just anyone out to make a desperate dollar. My experience has been that the surrogate was a giving person, a person who wants to help. If the right protocols guarding ethical relationships in the commercial surrogate industry are followed then even celebrities will be required to use the right person as a surrogate for their child.

3. Many mothers who bear and give birth to their own babies choose not to breastfeed. Not all babies are lucky enough to have a breast at their lips whether they are surrogate or not. There are options however such as expressing breast milk commercially. Again this is the parent's decision.
4. At 10 months of age my baby has been given a clean bill of health physically and psychologically. To come into this world a baby has to leave the womb. From my experience it did not matter that the hands carrying my child did not belong to the womb that did. What matters is the love I show my boy, that I keep him safe and nurture his development. My son knows I love him; he's no orphan.
5. A ban would make many people very sad especially knowing that it is possible but not allowed. A black market would inevitably evolve where ethics, monitoring and control wouldn't stand a chance. Parents, surrogates and babies will suffer far more in an underground surrogate industry.
6. A donated organ is gone for good once donated. The womb remains with the surrogate after the birth. Hiring a womb adds to human dignity if done the right way. But isn't that the same with everything? If it's managed well it is good. If it is managed badly then it is bad. As surrogacy is relatively new people need time to get used to the idea.
7. The successes of the surrogacy industry and the happiness it has brought to many thousands of good people must be promoted. News broadcasters do not normally make headlines with good news, it tends to be bad. So players in the ART industry need to address this and contribute a small portion of their revenues towards promoting the success story in the IVF/Surrogacy industry.

Dr. Nayna Patel
MD
IVF Specialist, Interviewed by Oprah Winfrey on her talk show about Surrogacy

1. In India, the society is dominated by men. The gender discrimination is at all levels which cause a woman to be vulnerable. Financial independence shapes the woman to get back their right &pride & help them to plan the future of her family. I am not averse to the fact that a woman (surrogate) is willing to give birth to one more additional child for a needy couple against financial benefit as long as surrogate is healthy. This cannot be equated to commercial organ donation where the donor parts with an important organ for getting commercial benefit.
2. Many celebrities either single or married have undergone surrogacy due to their personal justified medical reasons. As we are aware that due to their status, the negative angles of medical treatment taken by them are created by media for TRP rating.
4. It is left to the discretion of the commissioning couple whether they would like the surrogate to breast feed their biological child. Some centres do prepare the commissioning mother for breast feeding with medications.
5. The newborn baby is not aware who has nurtured her/him for 9 months in womb. It is the love and affection of the commissioning parents that make him/her very secured emotionally. When a preterm baby is in NICU for 3 months, does it feel half orphan? Do we oppose incubator care of preterm baby?
6. The ban on surrogacyis bound to affect the right to have a child for the couple who would have otherwise never given birth to their own baby without surrogacy. This violates the human right. Middle path would be to have appropriate law on surrogacy which will define –
   1. Amicable compensation a surrogate should have.
   2. Number of times a woman can act as a surrogate.
   3. To maintain central registry of surrogates.
7. Infertility is considered as a disease by the WHO and if medically indicated, a surrogacy should be allowed to be offered as a medical treatment. This cannot be equated with organ donation and should be treated as a separate entity.
9. Fully agree with the comments of listening to the benefits of surrogacy from successful commissioning parents.

Surrogacy Truths from the Horse's Mouth – the Surrogate

1. I do not find anything wrong with doing surrogacy in the first place. It was no coercion, and I do not have any regrets. I feel I have done a service to a childless couple and given them a gift of life! When it comes to criticizing, many people come forward and when it comes to helping, no body lends a hand. We all have reasons to do things, which are our own right reasons, and as long as they do not cause harm, why should other people judge us and decide on our behalf?
3. If asked to breastfeed, I would most willingly do so!
4. I was well prepared and well informed that it was actually not my child and that the child will be given to the actual parents and I am sure they have gone far to have this child and they will definitely love the child more.
5. I think the needy couples will go elsewhere and do it but we as underprivileged, uneducated women, we will not be left with many choices to make the much-needed money in any right way. I earned through surrogacy what I would probably earn with 10 years of wages. I got a home for my children and that is enough for a lifetime. I was well compensated for and paid everything promised by my treating doctors but maybe some surrogates face difficulties and get cheated, for that the government should enforce laws.
6. I feel I did rent my womb, but for my own need, and I did not beg, borrow and steal, or become a bar dancer or a commercial sex worker. Surrogacy and organ donation cannot be equated.

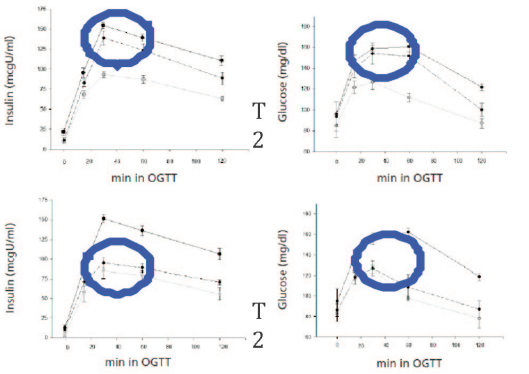
Inositols in PCOS

Maurizio Nordio
M.D., Ph.D.
Professor of Endocrinology and Internal Medicine. Department of Experimental Medicine, University "Sapienza", Rome, Italy. University UniPoliSI, Lugano, Switzerland

Even though Stein and Leventhal were the first of the modern era to describe the syndrome in 1935, an earlier description dates back to 1721, due to the italian Vallisneri who recognized "a young married peasant woman, moderately obese and infertile, with two larger than normal ovaries, bumpy, shiny and whitish, just like pigeon eggs". Despite the description, data of the literature suggest that Polycystic Ovary Syndrome (PCOS) is an ancient disorder, arising from ancestral gene variants selected during the Paleolithic Period and maintained over the past 10,000 years. Such ancient genes were likely transmitted transgenerationally through offsprings conceived between fertile carrier males and subfertile affected females.

Due to its high diffusion worldwide (it is one of the most common endocrine disorder in women of reproductive age) and to the fact that this complex syndrome affects fertility, metabolism and androgen status, the last decades were characterized by a huge number of studies in the attempt to better clarify its pathogenesis, leading to a more efficient approach in terms of therapy. In this view, the not-so-recent finding of an important involvement of insulin resistance in the syndrome is something that deeply changed the approach to PCOS patients. In fact, today it is well known that one of the most important traits of the syndrome is metabolic disruption and, in this view, insulin resistancehas become a distinctive pattern of the syndrome and can be detected in obese and lean women, independent of fat mass, in a high percentage of patients (65-70% of women with PCOS).The consequent hyperinsulinemia, thatis considered as a compensatory mechanism, has a direct stimulating effect onovarian androgen secretion, through a complex and multi-target mechanism involving the decrease of Sex Hormone Binding Globulin, the increase of LH bio-activity and IGF-1 availability at the ovarian cell level.In addition, hyperinsulinemia may also account for a series of important modifications of body functioning, as increased abdominal fat deposition, dyslipidemia, increased blood pressure, atherosclerosis, increased cardiovascular diseases risk and increased type II diabetes risk.Besides that, other factors such as ethnicity, genetic polymorphisms and thyroid autoimmunity should be taken into consideration when evaluating a patient with suspected PCOS. In this view, given that insulin resistance has a pivotal role in the syndrome, and therefore it should be considered more as a metabolic problem, rather than a reproductive one, the attention has focused on drugs that are able to correct hyperinsulinemia and other traits of the syndrome, such as metformin. This is the most widely used drug for type II diabetes and, since 1994, it is successfully used in PCOS treatment, in order to reduce the levels of insulin, in insulin resistant patients (those with PCOS included). However, its efficacy as infertility agent is still unclear, due to conflicting results from the literature and, in addition, side effects (mainly gastrointestinal) are also very possible. But science is always advancing its own knowledge and, in this effort, researchers realized in 2004 that metformin activity in PCOS and insulin resistant patients is performed through the increase of a second messenger that is called D-chiro-inositol. Therefore, scientists focused their attention upon the role of inositols in PCOS.

With the word "Inositol" is defined a family of nine stereoisomers that belong to the polyols family. The most relevant of these molecules are the so-called Myo-inositol (MYO) and D-chiro-inositol (DCI), with MYO being also the most abundant, accounting for about the 99% of all inositols. They received great attention by the scientific community as promising treatment for a wide series of pathological conditions, such as gynecological diseases, insulin resistance, psychiatric illnesses, and even cancer [1]. MYO and DCI exert a key role in controlling glucose homeostasis. In fact, MYO can be converted to DCI by the enzyme called Epimerase, which is activated by insulin, and its reduction is a crucial factor in the pathogenesis of PCOS. Both inositols are intracellularly incorporated into inositolphosphoglycans (IPGs), playing a key role as second messengers of insulin. However, their functions differ: MYO-IPGs mediate glucose uptake at the cellular level, while DCI-IPGs mediate glycogen synthesis. In fact, cells with a high glucose consumption rate (as brain and heart cells) contain high concentrations of MYO-IPGs, while DCI is mainly found in glucose storage cells (as liver, muscles and fat cells)[2]. Clinical observations demonstrated that DCI-IPGs concentration in muscle cells and DCI in urine of type II diabetic patients are lower than normal, whilst DCI being increased in the follicular fluid of insulin-resistant patients[3]. This discrepancy seems to depend on the fact that insulin resistance does not affect all tissues of the body. In fact, ovary and testis never become insulin resistant. Insulin resistance-derived hyperinsulinemia induces an increase in epimerase conversion activity, with the consequence of an increased DCI concentration into the ovary which, in turn, induces a drastic decrease in MYO intracellular levels, therefore explaining the altered ovarian function in hyperinsulinemic patients.Since the release of DCI-IPGs is decreased in all other tissues, different from the ovary, this may contribute to insulin resistance. Therefore, it is noteworthy that DCI administration is linked to the improvement of insulin sensitivity. In fact, PCOS patients receiving DCI, obtained an increase in insulin sensitivity after 8 weeks of treatment, thereby recovering the ovulatory function and decreasing parameters such as serum androgen concentration, blood pressure, plasma triglycerides, and increasing SHBG levels. A higher ovulation rate was also obtained in those patients, compared to the placebo group[4]. However, more recent studies outlined the fact that the use of DCI seems to be detrimental to the quality of oocytes and the ovarian response to FSH stimulation, in non-obese and non-insulin-resistant PCOS women.Interestingly, this effect was observed using the same amount of DCI of one of the previous studies[5]. Overall, data suggest that patients seeking for a pregnancy should not be treated with DCI, due to its negative impact on ovaries activity, while insulin-resistant PCOS women not interested in being pregnant might benefit from an adequate amount of DCI, especially if they have a family history of diabetes.



On the other side of the coin, due to the increase of epimerase activity into the ovary, MYO concentration is decreased in PCOS patients, thus explaining the decrease in oocytes quality and the alteration of folliculogenesis. In fact, MYO seems to play a crucial role in oocytes, accounting for about 99% of inositol intracellular pool. Thus, MYO may be considered as an important part of the follicular microenvironment and a valuable marker of oocyte quality, playing a pivotal role in both nuclear and cytoplasmic oocyte development. In accordance to that, studies showed that higher concentrations of MYO in the follicular fluid were correlated with good quality oocytes, in subfertile patients. Furthermore, MYO administration to women undergoing IVF was able to reduce the amount of recombinant follicle-stimulating hormone (r-FSH) used, improving the oocytes and embryo quality, as well as the implantation rate [6]. In addition, a number of studies demonstrated that the majority

Table I. Metabolic profile of the enrolled subjects at baseline and after 6 months treatment (means ± SD).

	Baseline	After 6 months treatment with myo-inositol plus D-chiro-inositol	*p* value
Age (years)	26.8 ± 5.1		
BMI	33.71 ± 6.1	33.1 ± 5.3	
Waist-hip ratio (cm)	0.92 ± 0.05	0.91 ± 0.09	
Tanita (% fat)	47.8 ± 4.4	47.1 ± 4.4	
BP systolic (mmHg)	121 ± 9.6	119 ± 8	
BP diastolic (mmHg)	71 ± 3.9	69 ± 8.5	
F. insulin (μU/ml)	18.2 ± 8.1	15 ± 8.7	= 0.05
F. glucose (mmol/L)	5.6 ± 0.5	4.7 ± 0.5	= 0.05
HOMA	5.8 ± 1.7	3.5 ± 1.1	= 0.05
T. cholesterol (mmol/L)	6.0 ± 1.8	5.01 ± 0.9	= 0.10
LDL (mmol/L)	3.5 ± 0.8	3.0 ± 0.8	= 0.03
TG (mmol/L)	2.0 ± 1.2	1.75 ± 1	= 0.24
HDL (mmol/L)	1.2 ± 0.2	1.3 ± 0.2	= 0.05

BMI: body mass index, BP: blood pressure, T. cholesterol: total cholesterol, LDL: low density lipoprotein, TG: triglycerides, HDL: high density lipoprotein, F. Insulin: fasting insulin, F. Glucose: fasting glucose.

of infertile PCOS patients respond to the oral supplementation of MYO with the restoration of spontaneous ovulation and menstrual cycles, together with an increase in progesterone levels during the luteal phase.It is noteworthy that MYO supplementation is also able to reduce both total and free testosterone serum levels, as already seen for DCI[7].

A few years ago, an important Consensus Conference on MYO and DCI in Obstetrics and Gynecology highlighted the principle that both MYO and DCI are critical molecules in PCOS treatment[8]. However, an important issue must be taken into account when deciding how to treat, due to the different effects of the two isomers that can be obtained when using different amounts and different ratios.

As an example, the ratio between MYO and DCI in the follicular fluid of normal women is 100:1 (MYO:DCI), and only 0.2:1 in PCOS patients, with significantly higher levels of LH, insulin resistance and hyperinsulinemia, thereby highlighting the importance of maintaining the physiological levels of these two isomers. In line with that above, our previous studies demonstrated thata therapy based upon the combined use of MYO plus DCI in an appropriate 40:1 physiological ratio seems to be a highly rational and effective approach to PCOS treatment. In fact, when the combination therapy (MYO 550mg + DCI 13.8mg in softgel capsule, twice a day) was administered to a group of overweight PCOS patients, during a period of 6 months, it resulted to be more effective than MYO alone(550mg in softgel capsule, twice a day) in terms of metabolic risk reduction. In particular, it was demonstrated that the combination therapy was able to induce a faster normalization of insulin and glucose responses to the Oral Glucose Tolerance Test (OGTT), achieving normal values right after three months of therapy, against the six months' period needed by the MYO only group of patients to ameliorate [9] (Fig. 1). In addition, in another study we demonstrated that the combination therapy in the 40:1 physiological ratio was able, besides decreasing insulin resistance and therefore the HOMA index, to also reduce the cardiovascular risk of overweight insulin resistant PCOS patients by the improvement of their lipid profile (LDL cholesterol decrease and HDL cholesterol increase) [10] (Tab. I).

In conclusion, the use of inositols in the therapy of PCOS is now widely accepted. Each of them has its own specific abilities. In particular, MYO demonstrates its efficacy in treating various aspects of PCOS, as well as gestational diabetes and metabolic syndrome, together with its extreme tolerability and lacking of those adverse effects that are so common using other drugs, as metformin and thiazolidinediones. The effectiveness of MYO and metformin, alone or in combination with rFSH was also tested for the treatment of menstrual irregularities, chronic anovulation, and infertility in PCOS patients. As a result, both drugs were considered as a first-line intervention in restoring normal menstrual cycles in most patients, with a higher level of efficacy for MYO, with no adverse effects, with respect to metformin.

DCI alone demonstrated its ability as insulin-sensitizer agent, and it has been shown to ameliorate metabolic abnormalities associated to insulin resistance in PCOS patients, improving glucose tolerance, reducing circulating insulin and decreasing serum androgen concentrations. However, DCI supplementation at a high daily dosage may be detrimental to oocyte quality and ovarian response. Therefore, the administration of the two isomers in the appropriate 40:1 physiological ratio has proven to be the most acceptable and safe solution for an efficient therapeutic approach to PCOS patients, in order to restore metabolic balance, prevent the development of pathologies as diabetes and cardiovascular diseases, and ameliorate fertility. Of course, such a great interest in these molecules grants from now on a large number future studies that are certainly needed using larger cohorts of patients, with a higher statistical power, in order to better clarify important issues as: the posttreatment outcomes using the different inositol isoforms; the evaluation of the variability of long-term outcomes on the basis of different PCOS phenotypes; the optimal therapeutic strategies tailored around the single patient.

Nevertheless, I like to conclude affirming all what is given above besides the fact that Pharmaceutical Companies should also guarantee that their products are of the highest available purity and quality, in order to give constantly high results and affordability. Keeping that in mind, I do believe that the administration of compounds that already belong to our organism (as Inositols) could be a modern, very efficacious and elegant approach to the therapy of PCOS patients, giving the body the chance to react by itself.

Relevant Literature

1. Bevilacqua A., Bizzarri M.: Physiological role and clinical utility of inositols in polycystic ovary syndrome. Best Pract. Res. Clin. Obstet. Gynaecol. 2016, 37:129-139.
2. Bizzarri M., Fuso A. Dinicola S., Cucina A., Bevilacqua A.: Pharmacodynamics and pharmacokinetics of inositol(s) in health and disease.Expert. Opin. Drug Metab. Toxicol. 2016, 12:1181-96.
3. Asplin I., Galasko G., Larner J.: Medical Sciences chiro-Inositol defi- ciency and insulin resistance: a comparison of the chiro-inositol- and the myo-inositol-containing insulin mediators isolated from urine, hemodialysate, and muscle of control and type II diabetic subjects. Proc Natl Acad Sci USA.1993, 90:5924-28.
4. Nestler J.E., Jakubowicz D.J., Reamer P., et al.: Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N. Engl. J. Med.1999, 340:1314-20.
5. Isabella R., Raffone E.: Does ovary need D-chiro-inositol? J. Ovarian Res.2012, 5:14.
6. Unfer V., Carlomagno G., Rizzo P., et al.:Myo-inositol rather than D-chiro-inositol is able to improve oocyte quality in intracytoplas- mic sperm injection cycles. A prospective, controlled, randomized trial. Eur. Rev. Med. Pharmacol. Sci.2011, 15:452-7.
7. Unfer V., Carlomagno G., Dante G., et al.: Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials. Gynecol. Endocrinol.2012, 28:509-515.
8. Bevilacqua A., Carlomagno G., Gerli S., et al.: Results from the inter- national consensus conference on myo-inositol and D-chiroinositol in obstetrics and gynecology-assisted reproduction technology. Gynecol. Endocrinol.2015, 31:441-6.
9. Nordio M., Proietti E.: The combined therapy with myo-inositol and D-chiro-inositol reduces the risk of metabolic disease in PCOS over- weight patients compared to myo-inositol supplementation alone. Eur. Rev. Med. Pharmacol. Sci.2012, 16:575-81.
10. Minozzi M., Nordio M., Pajalich R.: The Combined therapy myo-inositol plus D-Chiro-inositol, in a physiological ratio, reduces the cardiovascular risk by improving the lipid profile in PCOS patients.Eur. Rev. Med. Pharmacol. Sci. 2013, 17:537-40.

Endometrial Preparation for Thaw Embryo Transfer Cycle

Dr. Ameet Patki
MD,DNB,FICOG,FRCOG
Medical Director, Fertility Associates

Dr. Khyati Pandya
MBBS, DGO
Clinical Fellow Fertility Associates, Mumbai

Ovarian stimulation commonly results in the generation of more embryos than are necessary for the fresh embryo transfer cycle. Hence the need for cryopreservation and subsequent replacement of frozen thawed embryos. This is an integral part of assisted reproductive technique programs. In recent years, improvements in laboratory conditions and limitations on the number of embryos to be transferred have led to a progressive increase in Frozen-thawed Embryo Transfer (FET) cycles. This contributes to around 25% of all births achieved by ART. However, the best protocol for endometrial preparation in these cycles is still a matter of debate.FET prevents embryo waste and increases the probability of pregnancy in a single stimulated cycle. Protocols applied in FET cycles aim for endometrial preparation only and are therefore simpler than complicated protocols that aim to develop many follicles. Further, FET increases the cumulative pregnancy rate and decreases the cost; it is easy to perform and can be finished in a shorter time duration when compared to repetitive fresh embryo transfers. FET is also used after embryos obtained by implementation of in vitro maturation (IVM) in patients with severe polycystic ovaries wherein successful pregnancies have been achieved. Hence studies concentrate on factors affecting the success rate of FET cycles.

Embryo implantation represents the most critical step of the reproductive process in many species. It consists of a unique biological phenomenon, by which the blastocyst becomes intimately connected to the maternal endometrial surface to form the placenta that will provide an interface between the growing fetus and the maternal circulation. Successful implantation requires a receptive endometrium, a normal and functional embryo at the blastocyst developmental stage and a synchronized dialogue between maternal and embryonic tissues It is vital that a frozen - thawed embryo is replaced during the window of endometrial receptivity and that there is synchronization between embryo and endometrial development.There have been a number of different protocols developed to achieve this; namely –

- Replacement during a natural ovulatory cycle.
- Hormone (estrogen and progesterone) replacement cycles (with or without prior downregulation).
- Ovulation induction cycles.

There is evidence that endometrial receptivity may be negatively affected by ovarian stimulation. Although most clinicians earlier would advise fresh embryo transfer over FET, recent retrospective studies and a randomized controlled trials (RCTs) have suggested that there may be an advantage in freezing all blastocysts in the fresh cycle and replacing them in a natural or down regulated cycle. The finding of significantly improved pregnancy rates in a cryopreserved blastocyst cycle compared to the fresh cycle may be due to the improved endometrial receptivity and endometrial- embryo synchronization.

Natural FET Cycle

In FET cycle preparation, the easiest is the preparation of the endometrium during the natural cycle (NC) using the patient's own hormones. In this method, the timing for embryo transfer (ET) is determined by either determining the spontaneous luteinizing hormone (LH) surge or by the administration of exogenous hCG to start luteinization (Modified Natural Cycle, MNC). Success of the NC depends on the accurate determination of the ovulation time and the precise estimation of endometrial receptivity to detect the LH surge.Thawing and transfer procedures have to be performed during this receptive period. In the FET cycles performed during a natural cycle, urine or blood LH level is regularly analyzed and followed up.Ovulation is estimated to occur 36 to 40 hours after the presence of the blood LH surge. Urine LH increases 21 hours after the detection of the blood LH surge, and this fact has to be taken into consideration when interpreting the increase in urine LH. The NC-FET is becoming an increasingly common approach. The major advantage of replacement of embryos in a woman's natural ovulatory cycle is that no medication is required and the time taken to complete the cycle is short. However, there will be significant proportion of women in whom this approach will not be suitable like women with anovulatory PCOS.

Another problem is determining the time of the spontaneous LH surge, both among cycles and patients. At least one measurement, and preferably two measurements, has to be performed daily in order to accurately determine the LH surge. The threshold values of urine LH kits are highly variable, corresponding to an approximately 30% risk of a false-negative result; additionally, patients state that it is hard to interpret the test results.

Some clinics advocate the use of human chorionic gonadotropin (HCG) to trigger ovulation. A small RCT has shown that the use of an HCG trigger decreases the number of monitoring visits required in the natural cycle frozen embryo transfer with no difference in the pregnancy outcome. In NC or MNC, the embryo transfer is performed three to five days after ovulation, depending on when the embryos were frozen.

Ovulation may occur unexpectedly while planning an NC, which can lead to difficulties in adjusting the time of thawing and transferring the embryos. When an unexpected early ovulation occurs, the cycle is generally cancelled. In a study by Weissman et al, the LH surge was determined on the day of hCG administration during a modified natural cycle, and the cycle cancelled. However in previous studies, an LH surge on the day of hCG administration was shown not to exert any negative effect. A further RCT contradicted these findings and was terminated after interim analysis because of significantly increased ongoing pregnancy rate in the group having ET timed to the LH surge compared to those randomized to an hCG trigger. No RCTs have addressed the question of luteal phase progesterone supplementation in NC-FET, but a recent large retrospective study showed no benefits of luteal support in hCG triggered NCs.

Hormone Replacement Cycle

Another frequently used method for endometrial preparation is with the exogenous administration of estrogen (E) and progesterone (P), with or without a gonadotrophin-releasing-hormone (GnRH) agonist, also called the artificial cycle (AC), and is frequently used as an alternative to NC. Rates of clinical & biochemical pregnancy were shown not to differ in AC with regard to the administration of a GnRH agonist. One possible advantage of AC is that it allows flexibility as to the timing of embryo transfer that may suit both the patient and the clinic. A number of different protocols exist for ACs. First, ovarian down regulation can be achieved by using GnRH agonist, after which sequential E with subsequent addition of P is used.

Estrogens can be administered by various routes, i.e. oral, vaginal or patches/gel. No route has shown to have any clear advantages over others. However, amongst the compounds 17 b estradiol has advantages over estradiol valerate (EV), being more physiological and having less side effects. EV, when given orally is subjected to extensive first pass metabolism & converted into estrone, estriol & 17 b estradiol. Similarly P can also be administered by oral, vaginal or intramuscular routes. No route has shown to have any clear advantages over others. However oral Dydrogesterone has been shown to be significantly better in some recent studies. In order to mimic the endocrine conditions of a NC, E & P are administered consecutively. E administration is started at the beginning of the cycle before day 4, causing endometrial development while suppressing dominant follicle development. E administration is continued until the endometrium reaches a thickness of 8 mm (determined using an ultrasonographic examination), and P is then combined to initiate the secretory changes. Thus, an attempt is made to mimic

the physiologic mid-cycle E-P transition. In ACs, the time for thawing and transferring the embryos is planned according to the commencement of progesterone support. The exogenous administration of E & P does not guarantee the complete suppression of the pituitary gland; in other words, a dominant follicle may develop. The developing follicle may also undergo spontaneous luteinization, which leads to the early exposure of the endometrium to progesterone, and thus incorrect calculations for thawing and transfer times. For these reasons, GnRH agonists can be added to the treatment protocols in order to down regulate the pituitary, thus preventing follicular development. Both the ACs are less physiological due to exogenous drug administration; however, they are practical and easy to apply, and hence preferred both by physicians and patients. Four RCTs have evaluated the use of a GnRH analogue and subsequent hormone replacement compared to using E & P alone. A recent meta- analysis of that data showed no statistical difference in pregnancy rates, however, the only study to report live birth rates did show a statistically significant increase in the group which underwent down regulation prior to E & P supplementation. In a meta-analysis of studies comparing E & P with and without GnRH analogue, there was no significant difference in the cycle cancellation, endometrial thickness, or miscarriage rates.

Stimulated Regimes for FET Cycle

An alternative approach to endometrial preparation for the FET cycle is to use low dose ovarian stimulation. One RCT of 199 women compared the use of 150 IU FSH on day 6, 8 and 10 of the menstrual cycle to E & P endometrial preparation (with no prior downregulation). No differences were identified in the implantation or pregnancy rates, cancellation rate, or endometrial thickness. Clomiphene citrate has also been used for stimulation but the only RCT using this intervention showed no benefit over E & P, used with or without a GnRH analogue. Ovulation induction cycles have no benefits in terms of pregnancy rate. In addition, they require increased monitoring, are relatively expensive, and do not have the advantage of flexibility with regards to the timing of the embryo transfer.

ERA (ENDOMETRIAL RECEPTIVITY ARRAY)- This is a test that diagnoses the state of endometrial receptivity in the window of implantation in women. This molecular diagnostic tool is used to analyze the expression level of 238 genes related to the status of endometrial receptivity. The use of this test in patients with recurrent implantation failure (RIF) has shown that the window of implantation is displaced in a quarter of these patients and use of a personalized embryo transfer on the day designated by ERA improves reproductive performance. We also perform ERA in patients with persistently thin endometrium. Endometrial receptivity now appears to be the bottleneck of the reproductive process. Novel in vivo approaches, including additives to the embryo culture or intrauterine flushing with putative adhesion promoting factors, could potentially increase implantation rates especially in RIF patients. As an example, it has have shown that supplementation of recombinant heparinase to the embryo culture medium before transfer into mouse uteri significantly increases implantation rates. Endometrial biopsy samples can be used to identify molecules associated with uterine receptivity to obtain a better insight into human implantation. In addition, development of functional in vitro systems to study embryo-uterine interactions will lead to better define the interactions existing between the molecules involved in this process. Up to date, only a few modalities have been employed to treat failures of conception, despite the repeated transfer of apparently good quality embryos. The methods reported in the literature include medium supplementation by hyaluronic acid, systemic administration of LIF, progesterone, non-steroidal anti-inflammatory drugs like NSAIDs or heparin and others. With the exception of luteal phase support by progesterone administration, none of the treatments cited above was shown to be efficient in increasing implantation or pregnancy rates. Embryo implantation is the result of a well-orchestrated sequence of events including cellular adhesion, invasion and immune regulatory mechanisms, some of which are controlled through genetic processes by the ovarian hormones. It is rather surprising that during most days of the menstrual cycle, the endometrium is essentially hostile towards the embryo. A major physiological endeavor is thus needed by the endometrium so as to reverse this paradoxical condition.

References

- Andersen AG, Als-Nielsen B, Hornnes PJ, Andersen LF. Time interval from human chorionic gonadotrophin (HCG) injection to follicular rupture. Hum Reprod 1995; 10: 3202-5.
- Brinsden PR, Ndukwe G, Engrand P, Pinkstone S, Lancaster S, Macnamee MC and De Moustier B (2003) Does recombinant leukemia inhibitory factor improve implantation in women with recurrent failure of assisted reproduction treatment? O-050 ESHRE Annual Meeting, Madrid, Spain.
- Demirol A, Guven S, Benkhalifa M, Sari T, Gurgan T. Successful birth following transfer of frozen-thawed embryos produced from in-vitro matured oocytes. Reprod Biomed Online 2010; 21: 215-8.
- Dusterberg B, Schimdt-Gollwitzer M, Humpel M. Pharmacokinetics and biotransformation of Estradiol Valerate in ovariectomized women. Hormone Res 1985;21:145-154.
- El- Toukhy T, Taylor A, Khalaf Y, et al. Pituitary suppression in ultrasound monitored frozen embryo replacement cycles. A randomised study. Human reprod 2004; 19: 874-9.
- El-Toukhy T, Coomarasamy A, Khairy M, Sunkara K, Seed P, Khalaf Y, et al. The relationship between endometrial thickness and outcome of medicated frozen embryo replacement cycles. Fertil Steril 2008; 89: 832-9.
- Fatemi HM, Kyrou D, Bourgain C, et al. Cryopreserved-thawed human embryo transfer: spontaneous natural cycle is superior to HCG induced natural cycle. Fertil Steril 2010;94 :2054-8.
- Ghobra T, Vandekerchhove P. Cycle regime for frozen thawed embryo transfer. Cochrane Database syst rev 2008; 1: CD003414.
- Griesinger G, Weig M, Schroer A, Diedrich K, Kolibianakis EM. Mid-cycle serum levels of endogenous LH are not associated with the likelihood of pregnancy in artificial frozen-thawed embryo transfer cycles without pituitary suppression. Human Reprod 2007; 22: 2589-93.
- Groenewoud ER, Kollen BJ, Macklon NS, Cohlen BJ. Spontaneous LH surges prior to HCG administration in unstimulated-cycle frozen-thawed embryo transfer do not influence pregnancy rates. Reprod Biomed Online 2012; 24: 191-6.
- Imbar T, Hurwitz A. Synchronization between endometrial and embryonic age is not absolutely crucial for implantation. Fertil Steril 2004; 82: 472-4.
- Jaroudi KA, Hamilton C J, Willemsen WN, Sieck UV, Roca G. Artificial endometrial stimulation for frozen embryo replacement. Fertil Steril 1991; 55: 835-7.
- Kyrou D, Fatemi HM, Popovic- Todorovic B, et al. Vaginal progesterone supplement has no effect on ongoing pregnancy rate in hcg-induced natural frozen thawed embryo transfer cycle. Eur J Obs Gyn Reprod Biol 2010; 150: 175-9.
- Loh SKE, Ganesan G, Leong NK. Clomid versus hormone endometrial preparation in FET cycles. Abstract book of the 17th world congress in fertility and sterility (IFFS). Melbourne , Australia, 25-30 November 2001: 3. 2001.
- Maria Ruiz-Alonso, David Blesa, Patricia Díaz-Gimeno, Eva Gómez, Manuel Fernández-Sánchez, Francisco Carranza, Joan Carrera, Felip Vilella, Antonio Pellicer, Carlos Simón, The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure, Fertility and Sterility, Volume 100, Issue 3, September 2013, Pages 818-824.
- Miller PB, Soules MR. The usefulness of a urinary LH kit for ovulation prediction during menstrual cycles of normal women. Obstet Gynecol 1996; 87: 13-7.
- Nekoo EA, Chamani M, Tehrani ES, Rashidi BH, Tanha FD, Kalantari V. Artificial Endometrial Preparation for Frozen-Thawed Embryo Transfer with or without Pretreatment with Depot Gonadotropin Releasing Hormone Agonist in Women with Regular Menses. J Fam Reprod Health 2015; 9: 1-4.
- Nosarka S, Kruger T, Siebert I and Grove D (2005) Luteal phase support in in vitro fertilization: meta-analysis of randomized trials. Gynecol Obstet Invest 60,67-74.
- Nygren KG, Sullivan E, Zegers- Hochschild F, et al. International committee for monitoring assisted reproductive technology (ICMART) world report: assisted reproductive technology 2003. Fertil Steril 2011;95: 2209-22; 22e1-17.
- O'Connor KA, Brindle E, Miller RC, Shofer JB, Ferrell RJ, Klein NA, et al. Ovulation detection methods for urinary hormones: precision, daily and intermittent sampling and a combined hierarchical method. Hum Reprod 2006; 21: 1442-52.
- Pakkila M, Rasanen J, Heinonen S, Tinkanen H, Tuomivaara L, Makikallio K, Hippelainen M, Tapanainen JS and Martikainen H (2005) Low-dose aspirin does not improve ovarian responsiveness or pregnancy rate in IVF and ICSI patients: a randomized, placebo-controlled double-blind study. Hum Reprod 20,2211-2214.
- Park SJ, Goldsmith LT, Skurnick JH, Wojtczuk A, Weiss G. Characteristics of the urinary luteinizing hormone surge in young ovulatory women. Fertil Steril 2007; 88: 684-90.
- Patki AS, Pawar V. Modulating Fertility Outcome in Assisted Reproductive Technologies by The Use of Dydrogesterone. Gynaecological Endocrinology, 23(S1); 1-5 Oct 2007
- Paulson RJ. Hormonal induction of endometrial receptivity. Fertil Steril 2011; 96: 530-5.
- Revel A (2005) Implementation of integrin 3 level as predictor of implantation in an IVF program. ASRM/CFAS Annual Meeting, Montreal, Canada.
- Revel A, Helman A, Koler M, Shushan A, Goldshmidt O, Zcharia E, Aingorn H and Vlodavsky I (2005) Heparanase improves mouse embryo implantation. Fertil Steril 83,580-586.
- Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. Fertil Steril 96; 2: 344-8. 2004
- Simon A, Safran A, Revel A, Aizenman E, Reubinoff B, Porat-Katz A, Lewin A and Laufer N (2003) Hyaluronic acid can successfully replace albumin as the sole macromolecule in a human embryo transfer medium. Fertil Steril 79,1434-1438.
- Stern C, Chamley L, Norris H, Hale L and Baker HW (2003) A randomized, double-blind, placebo-controlled trial of heparin and aspirin for women with in vitro fertilization implantation failure and antiphospholipid or antinuclear antibodies. Fertil Steril 80,376-383.
- Weissman A, Horowitz E, Ravhon A, et al. Spontaneous ovulation versus HCG triggering for timing natural cycle frozen thawed embryo transfer: a randomised study. Reprod biomed online 2011;23: 484-9.
- Weissman A, Horowitz E, Ravhon A, Steinfeld Z, Mutzafi R, Golan A, et al. Spontaneous ovulation versus HCG triggering for timing natural-cycle frozen-thawed embryo transfer: a randomized study. Reprod Biomed Online 2011; 23: 484-9.
- Wright KP, Guibert J, Weitzen S, Davy C, Fauque P, Olivennes F. Artificial versus stimulated cycles for endometrial preparation prior to frozen-thawed embryo transfer. Reprod Biomed Online 2006; 13: 321-
- Wright KP, Guibert J, Weitzen S, et al. Artificial versus stimulated cycles for endometrial preparation prior to frozen thawed embryo transfer. Reprod Biomed Online 2006; 13: 321-5.

Block your Dates for ISAR's Forthcoming Events

(Details will Follow)

Annual YUVA-ISAR
Ahmedabad,
16th-17th December, 2017

Annual
ISAR – Embryology
Bhopal
4th-5th November, 2017

CMEs on
'Ovulation Induction & Luteal Support'
will be organized in all State Chapters

Master Training Workshop on
Managing the Subfertile Male & Male Sexual Dysfunction
Mumbai, 10th-11th Feb, 2018

ISAR-Ethicon Institute of Surgical Education/EISE (J&J)
2 Day Training Course in
Fertility-Enhancing Endoscopic Surgeries
for Postgraduate Students
to be held
every month, for 10 months, in Mumbai & Chennai, commencing July 2017.
Only 16 students per course per center

ISAR-Embryology Academy for Research & Training / EART
5 Day Course for Gynaecologists on Introduction to ART.
To include ovum pick-up & embryo transfer training on simulators!
July 2017- April 2018

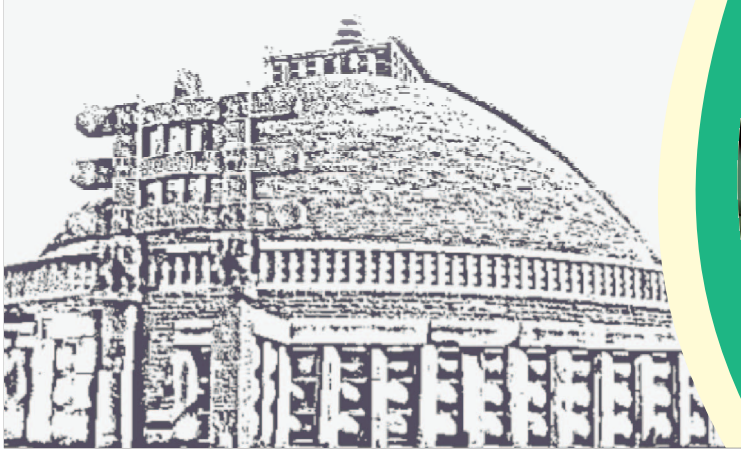
Postgraduate Digital Courses on
Practical Management of Infertility through Web streaming
10 sessions
in collaboration with
the PCOS Society &
Breach Candy Hospital, Mumbai
September 2017- January 2018

ISAR National Quiz
To be held nationwide for reproductive specialists under 40 years
Finalist in Plenary Session at
ISAR Congress, Kolkata, 2018
Fabulous prizes for Top three winners

EMBRYOLOGY ISAR-2017

isar
Indian Society for Assisted Reproduction

UNDERSTANDING
the SIMPLICITIES of
EMBRYOLOGY



EMBRYOLOGY ISAR-2017
CONFERENCE
4th & 5th NOVEMBER, 2017
BHOPAL

Registration details to follow

Join us at ASRM, San Antonio, USA for ISAR Symposium on

POLYCYSTIC OVARY SYNDROME AND FERTILITY: DO WE HAVE IT RIGHT?

November 1st, 2017, Wednesday

Time 3:30-5:00 pm

ISAR SYMPOSIUM

Dr. Ameet Patki	Prof. Duru Shah	Prof. Sadhna Desai
Can AMH predict response to ovarian stimulation?	Lean v/s Obese PCOS – does the IVF outcome differ?	How do we optimize ART results?

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Abbott

Women FIRST

The group that brought you the legendary progesterone

IF IT'S ORALLY EFFECTIVE IT'S †

duphaston®

Dydrogesterone Tablets IP 10mg

HAS SUPPLEMENTED IT'S RANGE

INTRODUCING

CYSTOFERT Chewables

Myo-Inositol 1100mg, Inositol 27.6mg (as D-Chiro-Inositol) Folic Acid 100mcg

THE PCOS Supplement

And has the only **oral 17 ß-estradiol**## identical to endogenous human estrogen[1]

℞ Estrabet

Estradiol (as Hemihydrate) Tablets USP 1 mg/2 mg

Along with another Pro in maternal care

℞ Pro® 9

Hydroxyprogesterone Injection IP 250 mg / 500 mg

The approved progesterone delivering full-term

IMS Dec 2016 accessed as on 04/04/2017. † Schindler AE. Progestational effects of dydrogesterone *in vitro, in vivo* and on the human endometrium. *Maturitas.* 2009;65(1):S3-S11.

Reference: 1. Schindler AE, *et al.* Classification and pharmacology of progestins. *Maturitas.* 2003;46(1):S7-S16.

Further information available on request from: Abbott India Limited, 3-4, Corporate Park, Sion-Trombay Road, Chembur, Mumbai 400071, India. www.abbott.co.in

INDCFT171154 05/18/2017