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Indian Society for Assisted Reproduction

The Newsletter of the Indian Society for Assisted Reproduction

isar Express

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

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Secretary General's Message

Dr. Ameet Patki
Secretary General, ISAR

Dear ISAR Members

It is my proud privilege to be the editor of our magazine ISAR Express. It is something I look forward too since it not only tells me advances in our specialty and keeps me abreast with what is happening in the world but also updates me on the various activities that ISAR is doing across the country.

We have selected a wide range of articles but tried to concentrate on two most important trends that we see in our routine practice both at the extreme of the spectrum namely ovarian senescence and OHSS. In addition we have a review article on the exhaustive literature on Progestogens in Infertility practice since implantation being the rate limiting step towards achieving a pregnancy and progestogens being closely associated with the same.

This issue also brings to you events from October 2017 where ISAR has participated, be it ASRM , Ethics meeting with ASRM or even the two Master Class programs conducted on Male Infertility (ADAM) and PCOS. In addition we have write ups on the Annual YUVA ISAR and ISAR Embryology conference.

By the time you read this issue the Annual ISAR conference at Kolkata must be on the way and I hope you all have participated and returned back to your practice with a few more Take home messages. As we always say we are here for the couples that are striving to achieve a pregnancy and ISAR will go all the way to help them achieve their dreams.

Do write back to us with your suggestions, views and what you would like us to do for you.

Regards

Dr. Ameet Patki
Editor ISAR Express
Secretary General, ISAR

For the **Winner** of the **ISAR Quiz**

Date: 22 February 2018

Dear ISAR Colleagues,

This year marks a significant milestone in the improving relations between the Indian Society of Assisted Reproduction (ISAR) and the European Society of Human Reproduction and Embryology (ESHRE). 2018 will prove to be a landmark year for the exchange of ideas and scientific knowledge between our two communities.

It is a considerable pleasure to accept the kind invitation from your President, Dr. Duru Shah, to provide the official and inaugural ESHRE Masterclass on practical aspects of ART at your prestigious ISAR Annual Conference in Kolkatta on 19th April. Reinforcing the goodwill, a second ESHRE session on single embryo transfer takes place on 21st April by three of our enthusiastic and dedicated ESHRE experts. This will hopefully bring our two societies more closely together and underpin increasing co-operation.

On behalf of ESHRE, we look forward to a long and sustained reciprocal exchange and, of course, the return of hospitality to your executive members in July 2018 at the ESHRE Annual Meeting in Barcelona.

All best wishes,

Dr. Roy Farquharson
MD FRCOG
ESHRE Chair 2017-19.

March 27, 2018

Congratulations on winning First Prize in the ISAR National Quiz! ASRM wishes to congratulate you and is offering you the following:

- Free Registration to ASRM 2018 Scientific Congress & Expo in Denver, Colorado, USA, October 6-10, 2018
- One Pre-Congress course of your choosing (fee waived for one course, hands-on courses excluded). Pre-Congress courses are on Saturday, October 6th or Sunday, October 7th.

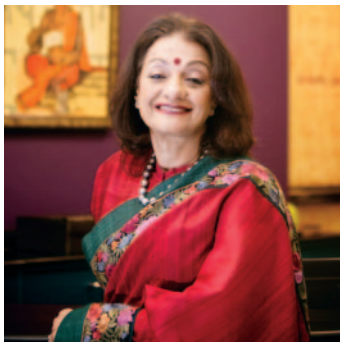
More information about the ASRM 2018 Scientific Congress & Expo, including a list of Pre-Congress courses and Scientific Congress sessions, can be found at our congress website:

https://scientific.asrmcongress.org/

Please email Jody Thrash, ASRM Education and Research Program Administrator, at jthrash@asrm.org to provide your name and email no later than June 1, 2018 so we can apply your complimentary course and registration to your account.

Congratulations again. We look forward to seeing you in Denver!

Richard Reindollar
M.D.
ASRM Executive Director



Dr. Duru Shah
MD, FRCOG, FCPS, FICS, FICOG, FICMCH, DGO, DFP
Director, Gynaecworld, The Center for Women's Fertility & Health, Mumbai
President, ISAR
Chief Editor, ISAR Express

President's Message

Dear Friends,

As I step down from the position of the President of the Indian Society for Assisted Reproduction, I am reflecting on whether I have done justice to the Chair which I occupied for a year. Have I completed the agenda which I set out to do and did I do it right? Did it make a difference to the people it was meant to make a difference to? Was I focused on my job or was I just enjoying the space I was in? It takes me back to the promises I made to myself and to you a year ago. I had dedicated my year to the E Cube –

Education, Ethics and Empathy.

I think **Education** stole the show because it reached out to thousands of young post graduates and clinicians, updating them on the latest in the field of Assisted Reproduction including Fertility Enhancing Surgery through Webinars, Travelling Seminars, Hands on Training and Masterclasses. Ovum Retrieval and Embryo Transfer was offered through Hands- on training on Simulators, embryo lab procedures such as preparation of a washed sperm sample, and handling of oocytes and doing ICSI on micromanipulators and finally endoscopic surgery on live animals tissue, all of which gave confidence to those who are just stepping into this field. We reached out to our post graduate students and our clinicians, all wanting to do the best for their patients, and to IVF specialists, updating them on the latest researchon the subject. Besides ISAR's members, we also reached out to about 30,000 gynaecologists who are not our members, through Webinars and our Quarterly Newsletters, which carried brilliant scientific articles from both National and International well-known personalities.

But the most important one which will continue is the **"START" Course,** (Simplifying Techniques in Assisted Reproduction Technology) an introductory Training Course for Assisted Reproduction, which will give the **right start in the right direction** to our young gynecologists who wish to train in ART.

The other important agenda has been to focus on **"Ethics"** in our clinical practice as there are boundless ethical issues in the field of ART. Whether to offer this technology to a woman of 60 years who is craving for a child, or to transfer more than 3 embryos while aiming for higher success rates, are all issues which are personal choices. But as clinicians offering the best of care and having taken the Hippocrates Oath of **"First do no harm"** we need to take a step back and do only what is ethically right. At ISAR we have created an Ethics Committee to create "Ethical **Guidelines"** with the assistance of international and national experts in the field of Bio-Ethics, Law, Research, Reproductive activitism, Religion, Obstetrics and Gynaecology along with Fertility management. We do hope these guidelines are read by our members to guide them on what is ethically right, when they are in a dilemma.

Our **ISAR- Ethics Committee** has done a brilliant job of adapting the ASRM and ICMR guidelines with the guidance of an International Expert in Ethics. Four Ethical Guidelines have been completed, and will soon be published and circulated. We do hope these guidelines which are focussed on ethical practices will be useful to all of you whenever you are in a dilemma on what is right for your patients.

The last but not the least on my agenda was to **Empathize** with our patients. I always wonder how women go through so much to have a baby! Their desire to be mothers is so extreme that they are willing to stretch themselves to any extent, may it be the daily injections, the time spent on treatment, giving up on their careers, the financial loss, the mental agony and many times extreme disappointment when the pregnancy test is negative after a long ordeal. I wanted to assist them in their journey, by making infertility treatment easier for them - by having it covered under their health insurance plan, which today is not covered at all! It is totally unfair that though infertility has been defined as a disease by WHO, it is still not on the radar of our country. I am happy to state that some States in our country have initiated the process, but we need much more, especially in our country where infertility is considered a taboo and causes immense emotional and psychological trauma. Unfortunately, even though I have knocked on many doors, I have not been able to even put a foot into the door to fulfil this motivation of mine, but will continue working on it, till I can, ultimately make a difference.

To reach out to our Society to raise awareness on **"Preventing Infertility"** we have created short 2 minutes videos uploaded on ISAR's You Tube and Facebook page **Better be safe than sorry** https://www.youtube.com/watch?v=eBaR7UCQ6rQ **Fighting the ticking clock** https://www.youtube.com/watch?v=L1PMXIH_vOE. These videos have been already seen by millions of young people, making them aware on what they should do to prevent infertility in future. A few more videos are in the making.

During my tenure as President, we have reached out to International Organizations such as ASRM and ESHRE, celebrated the first ISAR evening at ASRM, upgraded our Website which is the global face of our Organization, given a more aesthetic look to our Journal, and created the ISAR Flag with a brand new ISAR Logo, and will also hold ISAR's first Convocation!

Needless to say, this would not have been possible without a very strong team of dedicated workers of our Organization, and our corporate sponsors who walked with me all the way and I thank them immensely, because without them, all this would not have been possible!

I will step down as President ISAR on 20th April 2018 and hand over the ISAR Flag to the next President, offering all my support and best wishes towards an excellent tenure and a stronger ISAR.

I do feel happy that almost I could achieve most of what I had intended to do during my Presidential year. What I could not complete, I hope to complete in the year to come.

Thanking all of you for giving me this opportunity.

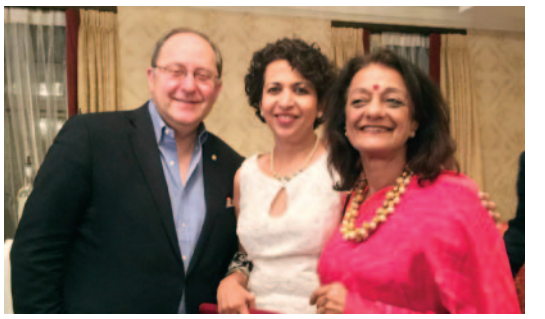
Duru Shah
President, Indian Society for Assisted Reproduction

ISAR at ASRM – 29th October-1st November 2017, San Antonio USA

ASRM this year had a good attendance from Fertility Experts from India.There were almost 60 doctors from India at the **ASRM**. On the 29th Evening Ansh Labs supported **ISAR India Evening** hosted by ISAR President Dr. Duru Shah and Gen Secretary Dr. Ameet Patki. Apart from ISAR members a large number of doctors from US, New Zealand, Europe attended the event. Prof Christopher the incoming ASRM President also graced the occasion. Mr. Gopal Savlani, Director Ansh Labs along with Dr. Anuja Dokras from ASRM spoke at the event. The Chief Guest Dr. Anupam Ray Counsul General of India Houston addressed the gathering from his residence since he was unwell and couldn't travel to San Antonio.

The next day 30th October India Special Interest Group (India SIG) conducted a Panel discussion on Optimizing ART outcomes. The Moderators were Drs Rishma Dhillon Pai, Kanthi Bansal and the Panelists were Drs. Hrishikesh Pai, Nandita Palshetkar, Sanjeeva Reddy, Rajul Tyagi, Kundan Ingale, Kaberi Baneerjee. It was well attended with a lot of interactive discussions.

On the 31st October Indian Reproductive Medicine Round Table Discussion was lead by Dr. Hrishikesh Pai on Premature Progesterone rise – Its Significance.



This was a lunch time symposium .

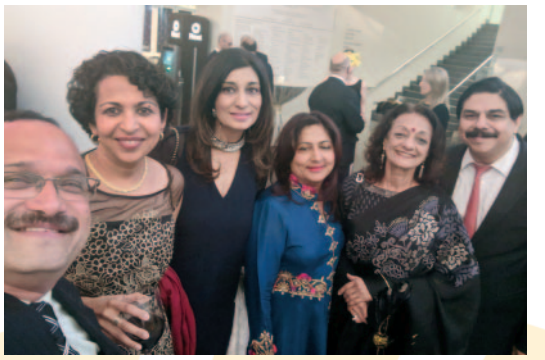
ISAR office bearers were invited for the President's Night Dinner where the Theme was Phantom of the Opera where exquisite masks were handed to guests. It was a night of Champagne , Fun and Dance.

On the 1st November The Main ISAR Session at ASRM was held on the Topic of PCOS and Fertility – Do we have it right ? the speakers were as follows

Dr. Ameet Patki – Can AMH predict response to ovarian stimulation ?

Prof. Duru Shah – Lean v/s Obese PCOS- Does the IVF outcome differ ?

Prof. Sadhna Desai – How do we optimize ART results



The large attendance at the session emphasized the importance of the topic .There was a good Q/A session at the end of the session which was well appreciated.

In summary **ISAR** had made a mark for itself at **ASRM** by its doctors presenting in Poster Presentations and various sessions spread across the full duration of the conference.

3rd National ISAR Embryology Conference – 27th-28th January 2018, Bhopal

3rd National ISAR Embryology Conference was held on 27th and 28th January 2018 at Bhopal.

The conference chairperson was Mr Virendra Shah and Organizing secretaries were Dr. Charudutt Joshi and Dr. Randhir Singh. Inauguration of the conference was done by State BJP President Mr. Nand Kumar Chauhan, ISAR President Dr. Duru Shah, ISAR Secretary Dr. Ameet Patki and members of the Organizing Committee.

On 27th January The President ISAR Dr. Duru Shah delivered the ISAR Embryology Oration on Clinical Aspects of IVF: What an Embryologist should know. The conference also had the first ever ISAR Embryology Qualifying Quiz in which 8 participants were selected for the National ISAR Embryology Quiz to be held at Kolkata. In the evening the banquet had entertainment program.

On 28th January 6 Interactive hands on workshops on various embryology topics were conducted. The conference and workshop had a total of 268 registrations.

YUVA ISAR 2017 – 15th-17th December 2017, Ahmedabad

YUVA ISAR, a unique national conference of the Indian Society of Assisted Reproduction hosted by the Gujarat Chapter of ISAR held in Ahmedabad on 15th 16th and 17th December 2017. **YUVA ISAR** conference was organized by Gujarat Chapter ISAR (GC-ISAR) in association with ISAR (Indian Society of Assisted Reproduction) & AOGS (Ahmedabad Obstetrics & Gynaecological Society). Organizing Chairperson, Dr. Kanthi Bansal & Organizing Secretary, Dr. R. G. Patel and the organizing team of **YUVA ISAR** work together to make the conference a huge success.

Around 150 doctors from all over India and 5 invited International doctors participated in the conference for sharing their knowledge & experience with the young doctors. The conference made a record registrations of 600 delegates in **YUVA ISAR** till date.

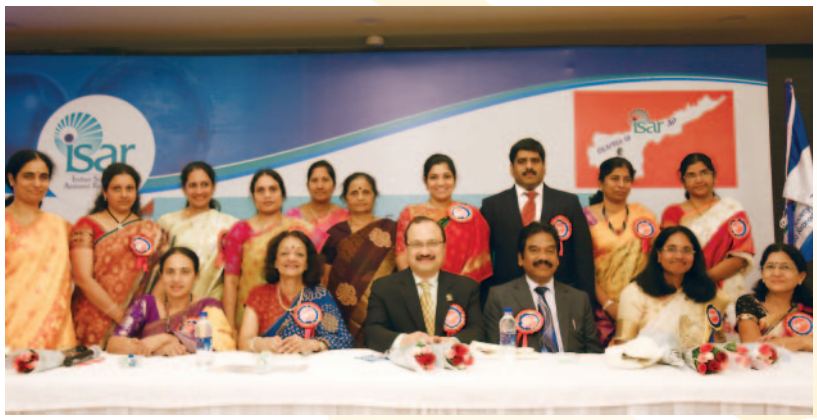
The theme of the conference was "YUVA-Illuminate Fertility Enhancement". The Scientific program was planned according to the theme. It covered all the aspects from Basics to advances of embryology, infertility & ART. There were three Workshops namely Tips & Tricks of Embryology, Tips & Tricks of Sonography & Tips & Tricks of Clinical ART. The workshop was on 15th December 2017 and the Conference was on 16th & 17th December, 2017 which included the entire subject of Embryology, Infertility and ART. The program included 9 keynotes and 1 oration in addition to 10 oral presentations and 6 Poster presentations. 80% of the faculties were young doctors under 40 years.

The cultural program was another highlight of the conference. It was a magical music night with Sa Re Ga Ma fame artists and Hindi film musicians.

The inaugural function was held on 16th December from 12 pm to 12.45 pm in presence of President of ISAR, Dr. Duru Shah, Secretary of ISAR Dr. Ameet Patki, Organizing Chairperson Dr. Kanthi Bansal Organizing Secretary Dr. R. G. Patel. Our Honourable Chief Guest "Dr. Manjula Pooja Shroff, An Edupreneur" CEO of Kalorex and Guest of honour "Ms. Kaajal Oza Vaidya" Novelist – Columnist – Literature Faculty. The inauguration was started with a prayer by our own Dr. Lalit Prabha and lighting of lamp and hoisting of our ISAR flag.

ISAR National Quiz was organized on 17th December in which 41 doctors participated.

Inauguration – Andhra Pradesh Chapter-ISAR – 4th February, 2018



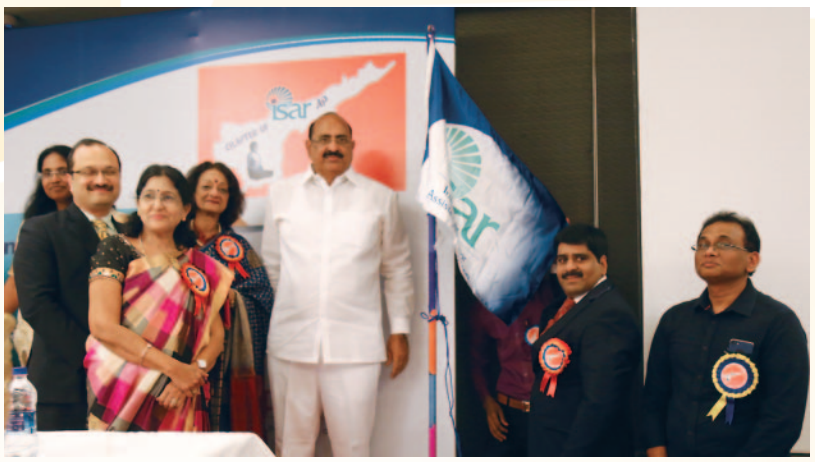
ISAR chapter in **Andhra Pradesh** was inaugurated at Vijayawada, Hotel Taj Gateway on 4th February, 2018 .

The Health minister Honourable Dr. Kamineni Srinivas unfurled the newly designed ISAR flag to formally launch the chapter in the august presence of the President ISAR, Dr. Duru Shah, Secretary General ISAR, Dr. Ameet Patki, Along with the Secretary of Tamil Nadu and Pondicherry chapter of ISAR, Dr. Sanjeev Reddy.

The inauguration was a great success with 200 members – gynaecologists and post graduates from all over Andhra Pradesh attending this program. This was followed by 6 interactive lectures and a panel discussion with distinguished experts. The program ended with an interesting quiz .

The office bearers installed unanimously for the Executive committee are – President: Dr. V Padmaja, Vice president: Dr. Sudha Padma Sri, Secretary: Dr. Chandana V, Treasurer: Dr. Kavithach, Joint secretary: Dr. Padma S.

Many senior Gynaecologists from all over Andhra Pradesh were present for the installation and bless the office bearers.



Progestogens in Infertility Practice

Dr. Ameet Patki
MD, DNB, FCPS, FRCOG(UK)
Medical Director
Fertility Associates Mumbai
Sec. Gen. ISAR

Dr. Krutika Makhija
MBBS, DNB
Reproductive Medicine
Specialist, Formerly Fellow
Fertility Associates

Progesterone is a natural steroidal hormone (21 carbon steroid) derived from cholesterol. It is secreted primarily from the corpus luteum of the ovary during the second half of the menstrual cycle and from the placenta during pregnancy. Chemically progesterone is a pregn-4ene-3, 20-dione. The word progesterone is derived from the Latin word 'Gestare' meaning to bear or carry. It is also believed that the name progesterone is derived from progestational steroidal ketone. Natural progesterone is rapidly metabolized and inactivated when administered by oral route so it is to be used parentally. A number of compounds are synthesized having progesterone like activities and can be given orally. These are called progestational agents, progestogens or progestins. Natural progesterone is now available in micronized form, which can be administered orally.

Progesterone was recognized early on to be one of the most important steroids required for the maintenance of pregnancy. Its role in mammalian reproduction is well described and is undisputed. The ability of the mother and the fetus to co-exist as two distinct immunological systems results from endocrine, paracrine and immunological modification of fetal and maternal tissues. The exact role of progesterone in this immunological modification has remained elusive.

Progesterone: A Pro-pregnancy Molecule

High local concentration of progesterone is important because of the known multiple effects of this hormone on reproductive system cells and extra-reproductive organs such as breast, brain and bone. After ovulation, progesterone secreted by corpus luteum induces transformation of the proliferative endometrium into the secretory type required for implantation. It undergoes specific morphological changes, which are termed 'decidualization'. All cellular types and structures localized in the functional layer are targets of progesterone action, namely, stromal cells, epithelial glands, and spiral arteries. However, another aspect of progesterone role in successful pregnancy is worth detailed consideration and that is its immune-modulatory effects.

Pregnancy: Immunological Phenomenon

Pregnancy contains antigens contributed by the father, which are foreign to the mother. Thus, the mother must adapt her immune response so as not to reject or destroy the conceptus. However, even as the maternal immune system has to tolerate the contribution of paternal antigens, it must maintain anti-infectious immune responsiveness to protect both the mother and the conceptus. Pregnancy has therefore been thought to be a state of immunologic tolerance. This tolerance is assumed to result from signals given by the conceptus to the mother's immune cells.

There is increasing evidence that progesterone is a key modulator in the immune response required to achieve a successful pregnancy outcome. The complexities of the adaptation between the maternal immune system and the semi allograft of the feto-placental unit are not clearly understood. The presence of progesterone and an up regulation of its receptors on decidual natural killer cells (DNK) and placental lymphocytes appears to be required to defend the developing trophoblast from the maternal immune reaction. These activated cells then synthesize progesterone-induced blocking factor (PIBF), mediating both the immune-modulatory and anti-abortive effects of progesterone. It is important to understand the immunological interplay that occurs during the implantation to understand the levels where the progesterone affects the immunological acceptance. Immune response can be divided into two activities: an innate immune response and an adaptive (or acquired) immune response.

Innate Immune System

The innate immune system is an ancient mechanism of host defense found in essentially every multicellular organism from plants to humans. It serves as the body's first line of defense that comes into play immediately or within hours of appearance of the antigen in the body. The cells involved in innate immune responses include NK cells. Natural killer cells are a type of immune cells that are called lymphocytes. Natural killer cells secrete different proteins or cytokines depending on the signal they receive. If this first line of defense is not successful in neutralizing the potential harmful invader, the adaptive immune system is signaled.

Adaptive Immune System

The adaptive immune system is slower and more complex than the innate immune response. The antigen must first be processed and recognized. Once an antigen has been recognized, the adaptive system activates immune cells specifically designed to attack that antigen. The cells involved in the adaptive immune response include both T and B lymphocytes.

T-cells

T-cells are a subset of lymphocytes that play a large role in immune responses. The abbreviation 'T' stands for thymus. Most of the T-cells in the body belong to three subsets:

1. Cytotoxic T-cells: These T-cells express on their surface an antigen called CD8. The role of cytotoxic T-cell is to monitor all cells in the body and to destroy those that express foreign antigens.

2. Helper T-cells: These T-cells express on their surface CD4 antigens and function as 'middle-men' in immune responses. When activated, helper T-cells proliferate and secrete proteins called cytokines that regulate or 'help' other lymphocyte function. There are two kinds of cytokines secreted by T helper cells, pro-inflammatory cytokines that are largely involved in cell-mediated immunity (called Th1 responses) and anti-inflammatory cytokines that are involved in promoting B-cells to secrete antibodies (called Th2 responses).

3. Regulatory T-cells (also known as suppressor T-cells): These T-cells suppress activation of the immune system. Regulatory T-cells express the cell surface antigens of CD8 and CD25. Failure of regulatory T-cells to function properly may result in autoimmune disease in which the immune cells attack healthy cells in the body.

B-cells

B-cells, when activated, secrete proteins called antibodies. Antibodies inactivate antigens by several mechanisms:

1. Complement fixation (proteins attach to antigen cell causing lysis).
2. Neutralization (binding to specific sites to prevent attachment).
3. Agglutination (clumping).
4. Precipitation (forcing insolubility and setting out of solution).

B-cells and antibody activity have been referred to as 'humoral immunity' whereas T-cells activity has been called 'cellular immunity'.

The Fetal Tolerance

The conceptus is a semi-allogenic graft, because it is produced by the contribution of both the mother and the father. Although fetal allo-antigens encoded by genes, inherited from the father should provoke maternal responses and lead to fetal loss, normally this does not happen. This natural miracle, known as the 'immunological paradox' of pregnancy, is considered to be the result of a particular immune response of the pregnant woman.

Cytokine Immune Mediators

The fetal tolerance is a facilitation reaction or the enhancing effect which is characterized by a predominance of humoral responses, which may counteract the rejection reaction and have a beneficial effect on the antigenic target. Predominance of this facilitation reaction over the rejection reaction appears in pregnancy, where enhancing non-complement-fixing antibodies and suppressor cells favor the acceptance of the embryo because they prevent complement-mediated cell lysis while they block allogeneic reactions, either by covering the allo-antigens or through the function of an 'idiotype anti-idiotype' antibody network. If the co-existing but suppressed rejection reaction is upregulated, the embryo is rejected. The suggestion that the facilitation reaction prevails over the rejection reaction and succeeds in immune tolerance has been followed by many studies which have concentrated on the mechanisms mediating this particular response.

Shift of the Cytokine Balance

The 'immunotrophic theory' presented by Wegmann in 1987 stated that the normal development of the placenta is the result of the influence of cytokines. The

cytokines implicated were placenta immunotrophic cytokines such as granulocyte-macrophage colony stimulating factor (GM-CSF), transforming growth factor-b, and interleukin-3(IL-3). During pregnancy there is a change of the Th1/Th2 equilibrium so that the Th2 type cytokines (IL-4m IL-5, IL-10) predominate over Th1-Type cytokines (IL-2 and interferon g[IFN-g]) and benefit the developing embryo by enhancing placental growth and function as well as by preventing inappropriate anti-trophoblastic cytotoxic reactions. Heat shock proteins (Hsp), pregnancy specific b1-glycoprotein, and increased expression of the nonclassical major histocompatibility complex (MHC) class I human leukocyte antigen (HLA)-G molecule have been suggested to stimulate endometrial macrophages for IL-10 production, which enhances the Th2 shift.

Progesterone: Direct Influence on Immune Responses

It has been shown that progesterone induces changes in the functions of a number of immune-competent cells by different molecular and cellular mechanisms. It stimulates the activity of some specific enzyme matrix metalloproteinases. and adhesion molecules, 10 inhibits antibody production and suppresses T-cell activation and cytotoxicity and directly or indirectly modifies the activity of NK cells, which are the most numerous lymphoid cells locally.

Progesterone-induced Blocking Factor

Human chorionic gonadotropin (hCG) produced by the trophoblasts induces the production of progesterone by the corpus luteum. Through an immune-regulatory protein known as progesterone-induced blocking factor (PIBF), progesterone may induce the production of IL-4BY g/d T lymphocytes and thus, enhance the Th2 response.

Progesterone Receptors and Hypothesis of Fetal Immune Acceptance

Progesterone receptors (PgR) are found on the T-lymphocytes in normal pregnancy, but at a lower density than other progesterone target receptor tissues. They are not demonstrated in normal T-lymphocytes. Liver transplant and blood transfusions are known to induce PgR on g/d T-cells, even in males. Paternal lymphocyte injection prior to ovulation has been shown to increase PIBF expression in the mid to late luteal phase in women exposed to embryo transfer.

The above observations explain the way in which the fetus escapes immune rejection by the NK cells. Thus, one can state the hypothesis that the fetal semi-allograft following trophoblastic invasion induces PgR in y/Q T-cells. The interaction with high concentrations of progesterone causes the expression of PIBF by the g/d T-cells with induced PgR. The PIBF is only made at the maternal fetal interface as this is where the progesterone concentration is adequate. The suppression of the cellular immune system is limited to the maternal-fetal interface, and this constitutes selective immune tolerance.

Progesterone acting via Dendritic and Mesenchymal cells

Immunomodulatory effects of progesterone on other seemingly less-observed cell populations engaged in the immune response control during pregnancy, such as dendritic cells and mesenchymal stem cells have also been studied.

Dendritic Cells

Dendritic cells are the professional antigen-presenting cells and thus, they are the key factors in initiating the afferent arm of the immune response related to antigen recognition. Dendritic cell functions include secretion of a number of cytokines that actively regulate various key populations of immune cells. The presence of monocyte-derived dendritic cells in human decidus has been reported.

There are numerous data about the immunoregulatory role of dendritic cells and it has been proposed that in pregnancy the dendritic cells regulate Th1/Th2 bias by secreting IL-12 because myeloid dendritic cells would cause Th1 predominance and possible abortion.

Mesenchymal Stem Cells

Mesenchymal stem cells are widely spread in the body yet it has been shown that they are located perivascularly in human endometrium, which would suggest their active participation in building up the structure of human decidua. It is supposed that under the influence of progesterone, which is in high local concentrations, these cells are induced to express HLA-G and to secrete the constitutively expressed PIBF and thus, participate in a very well-tuned immune response in pregnancy.

Luteal Phase Insufficiency

The term luteal phase deficiency was first coined more than 60 years ago and, since then it has been suggested as a clinical entity per se and an etiological factor for subfertility, implantation failure, and recurrent miscarriage. Evaluation of luteal phase and progesterone therapy is commonly used in daily practice despite the recommendations for rational work-up in subfertility. Pregnancy establishment in mammals requires prolongation of luteal life span and progesterone production. Progesterone stimulates secretory functions of the endometrium, which is required for the development and implantation of conceptus. The pregnancy recognition signals secreted by the conceptus may be luteotrophic, if they directly maintain corpus luteum (CL) function, or antiluteoytic, if they decrease uterine release of luteolytic prostaglandin F (PGF2a).

The period from occurrence of ovulation until the establishment of a pregnancy or the resumption of menstrual cycle 2 weeks later is known as the luteal phase. Normal luteal function requires optimal pre-ovulatory follicular development, luteinization of the granulosa cells to produce progesterone, continued tonic lutenizing hormone (LH) support, vascularization of the corpus luteum (CL), and estrogen to induce progesterone (P4) receptors in the endometrium. A normal life span of the CL is 14 days unless rescued by human chorionic gonadotropin (hCG) secreted by developing blastocyst after implantation. Maintenance of the CL and its secretions is mediated by hCG which is produced by the embryo. By inducing secretory changes, following adequate estrogen priming, progesterone induces a normal endometrial receptivity.

From the patients' last menstrual cycle, the 7th gestational week is the period of the estimated onset of placental steroidogenesis (the luteo-placental shift).

In normal ovulatory sub-fertile women, 92% of cycles show normal luteal function and luteal support therefore seems unnecessary. Luteal phase insufficiency generally stems from an insufficiency of estrogen and P4 production after ovulation. This insufficiency is due to the inhibition of the LH in the early luteal phase by steroids secreted in supra-physiologic doses in stimulated cycles. If luteal phase hormonal support is not present in assisted reproduction technique (ART) cycles, the serum estrogen and P4 levels drop, thus leading to a decrease in the implantation rates and pregnancy rates.

Human folliculogenesis and CL function are controlled by pituitary gonadotropins.

Follicle stimulating hormone (FSH) is responsible for the selection of the dominant follicle, while LH stimulates the production of androgens from the theca cells and sustains the growth of the selected follicle during the second half of the follicular phase. At mid-cycle, the gonadotropin surge has important physiological roles, including induction of luteinization of the granulosa cells, resumption of oocyte meiosis, rupture of the pre-ovulatory follicle, and formation of the CL. Among other events, post-LH surge changes include a shift in steroidogenesis within the follicle with a marked decrease in estradiol (E2) concentrations and a gradual increase in serum progesterone concentrations.

Additional alterations involve uncoupling of gap junctions between granulosa cells and the plasma membrane of the oocyte, a process that seems to be important for the resumption of meiosis.

For the transfer of cholesterol from the outer to the inner surface of the mitochondrial membrane steroidogenic acute regulatory protein (STAR) is important 30 The STAR protein is absent from the granulosa cells before the onset of the LH surge and this explains the inability of these cells to produce progesterone.

Formation of the Corpus Luteum

The CL is formed from the remnants of the ovulated follicle and contains a heterogeneous population of cells including steroidogenic cells, fibroblasts, immune cells, and endothelial cells.

The steroidogenic cells are the large and the small luteal cells that are derived from the gtranulosa and the theca cells of the ruptured follicle, respectively.

An important step in the formation of the CL is the neovascularization, a process that is characterized by the invasion of the granulosa layer by new vessels. The granulosa cells of the pre-ovulatory follicle are not vascularized, since blood supply is terminated at the basement membrane. Following ovulation, basement membrane integrity is lost, tissue re-modeling takes place and vessels, originating from the thecal vasculature, invade the granulosa-luteal cells .

Over the next few days, intensive angiogenesis takes place and a capillary network extends throughout the fully differentiated CL tissue. In humans, both vascular

density and endothelial area of each vessel increase markedly from the luteinized granulosa cells of the early CL to the mid-luteal stage. Neoangiogenesis is important for the CL function and is controlled by various angiogenic factors, such as vascular endothelial growth (VEGF), fibroblast growth factor, angiopoietins, and insulin-like growth factors vitro data in the macaque have shown that the expression of VEGF mRNA in CL tissue increases significantly from the early to the mid-luteal phase and decreases in the late luteal. (18)

The process of neovascularization is regulated by pituitary LH. (19) Luteinizing hormone activates matrix metalloproteinases that degrade exztracelluar matrix associated with the blood vessels. The CL produces progesterone, estrogens, and non-steroidal substances, such as inhibit A. Luteinizing hormone is the main luteotrophic hormone that stimulates the production of progesterone. Apart from the pituitary gonadotropins, different local substances may also regulate the CL life span and function. Such substances include growth factors, preptides, steroids, and prostaglandins.

Progesterone in Implantation and Early Pregnancy

Normal luteal function is essential for maintaining pregnancy. Secretory transformation of the endometrium in the luteal phase is induced by progesterone and after adequate estrogen priming, it improves endometrial receptivity. In endometrial receptivity the endometrial epithelium acquires a functional and transient ovarian steroid-dependent status, which allows blastocyst adhesion and it is a self-limited period.

The complex Molecular interactions between the hormonally-prime uterus and an activated blastocyst results in the successful implantation. The role of steroid hormones is the best understood among the many aspects of the synchronization process. The proliferation and differentiation of uterine epithelial cells is promoted by the pre-ovulatory increase in the secretion of 17B-E2, and it is followed by the production of progesterone. Progesterone induces the proliferation and differentiation of stromal cells. Progesterone receptor synthesis is controlled by estrogens through estrogen receptors during the proliferative phase. If the synthesis of the estrogen receptors is inhibited then progesterone leads to a fall of both estrogen and progesterone receptors. Various experimental studies reported down regulation of progesterone receptor epithelial cell expression during the luteal phase of the menstrual cycle.

Local vasodilatation and uterine musculature quiescence is also promoted by progesterone by inducing nitric oxide synthesis in the deciduas. A study of in vitro fertilization (IVF) embryo transfer outcomes support the uterine-relaxing properties of progesterone. This study with the help of ultrasound during embryo transfer investigated the consequences of uterine contractions (UC) and is also visualized during this time. Results showed that on the day of embryo transfer a high frequency of UC hindered the transfer outcome, possibly by discharging the embryos out of the uterine cavity. The benefits of progesterone in IVF are found as there was a negative correlation between UC frequency and progesterone concentrations was found.

For the low implantation rates in IVF decreased endometrial receptivity is largely responsible. Physiological and morphological changes of the endometrium are triggered by estrogens and progesterone secreted cyclically by the ovary that creates a suitable endometrial environment for the implantation of embryo and maintenance of early pregnancy. Thus, progesterone has a very important role in implantation and maintenance of early pregnancy. Progesterone-receptor antagonists induce abortion if given within the first 7 weeks of pregnancy. Similarly, an abrupt decrease in serum progesterone concentrations followed by miscarriage is found when surgical removal of the ovary is done with the CL of pregnancy before 7 weeks of gestation.

Luteal phase deficiency results from the decrease in the amount or the duration of progesterone secretion by the CL, or the lack of an adequate response by the endometrium.

There may be two types of luteal phase defect (LPD): one related to the presence of immature follicles, and one where the follicles are mature. In both types, supplemental therapy with progesterone is effective in creating a healthy uterine environment.

In women who undergo ovulation induction, multiple follicles of different size might ovulate at different times, thus expanding the fertilization window. It can be expected that sex steroid concentrations, both estradiol (E2 and progesterone, after multiple ovulation will be significantly higher.These high concentrations may not only influence the receptivity of the endometrium, but may also cause luteal insufficiency as high concentrations of steroids through negative feedback on the pituitary-hypothalamic axis, inhibit the production of luteal LH, mandatory for luteal progesterone production.

It was found that there was significant negative correlation between both pre-ovulatory E2 and day 16 progesterone and the concentration of cytosolic progesterone receptor (Cpr), while advanced endometrial maturity tends to be associated with low concentrations of cPR. Further, natural cycles were characterized by low cytosolic E-2 receptors (cER) and high cPR, whereas the concentration of both receptors was greatly reduced in stimulated cycles.

Due to receptor abnormalities, the endometrium can be progesterone deficient even if plasma progesterone levels are normal. According to a study it was suggested that in approximately 25% of women with recurrent miscarriage, the spatial expression of progesterone receptors in the endometrium is different from that in normal controls.

Impaired reproductive function and early abortions are caused due to mutations in the progesterone receptor gene. A study demonstrated a polymorphism within the coding sequence of the human progesterone receptor gene that occurs at a significantly higher frequency in patients with recurrent miscarriages than in controls. These findings support the fact that in recurrent first-trimester spontaneous miscarriage absolute or relative progesterone deficiency as a biologically significant factor is existing. Also progesterone supplementation should potentially be successful in the former cases. P4 treatment may not prove to be beneficial in the women suffering from relative progesterone deficiency. Several studies reported that recurrent miscarriages patients with delayed endometrium showed lower than normal serum progesterone concentrations, when compared to those with normal endometrium, whereas significant differences between the two groups in others is not detected.

Apart from implantation failure and higher miscarriage rates the incidence of ectopic pregnancy was also higher in patients with LPD whose infertility was due to anovulation. The ectopic pregnancy and spontaneous abortion rates also were higher in patients with LPD who were untreated than in those who were treated.

Management

A delayed endometrial development, as noted on endometrial biopsy in at least two cycles; and a low mid-luteal serum progesterone concentration are considered diagnostic of LPD. Stress and excessive exercise can induce LPD, which may not require any medical intervention apart from appropriate counselling. Abnormalities of the luteal phase are found in 3-10% of the female population with primary or secondary infertility and in up to 30% of women with recurrent pregnancy loss (RPL). Latrogenic LPD is seen with the use of controlled ovarian stimulation (COS), and gonadotropin-releasing hormone (GnRH) analogues for in vitro fertilization (IVF), and intrauterine insemination (IUI) cycles. Latrogenic LPD has provided an opportunity to study the endocrine and endometrial abnormalities during the luteal phase and the impact of any pharmacological intervention.

Management of LPD in Art

It is well established that IVF cycles are associated with LPD. Various reasons include supraphysiological steroidogenesis, follicle aspiration leading to depletion of granulosa cells, suppression of LH in luteal phase, and delayed pituitary recovery in GnRH agonist (GnRHa) cycles. It was believed earlier that incorporation of antagonists into IVF cycles will obviate the need for any luteal phase support. However, it soon became evident that antagonists lead to premature luteolysis.

Human Chorionic Gonadotropin

The earliest form of treatment has been supplementation of luteal phase with small doses of human chorionic gonadotropin (hCG). Of the various mechanisms by which hCG can rescue the corpus luteum (CL), an increase in both E2 and progesterone levels appears to be the most obvious effect. Usual dose is 1500-2500 IU twice a week from the day of embryo transfer (ET) continued till the day of pregnancy test or till 8-10 weeks of gestation. Meta-analyses comparing hCG with progesterone have shown it to be associated with either better or at least similar pregnancy rates to that seen with progesterone.

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Can we Prevent Ovarian Senescence?

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Natural female reproductive cycle

The female ovaries have a natural cycle of growth and senescence which culminates in menopause around the late 40s or early 50s .The decline in reproductive function starts by age 35-37.

The number of germ cells that arrive at the genital ridge (future ovaries) is not more than few hundred; however, they divide rapidly to form 10,000 oogonia by six weeks of gestation.The number further rises to 600,000 by the eighth week and to 6-7 million by twentieth week of gestation.However, after 20th week (midgestation), the number of oocytes rapidly decline for two reasons, first is decreasing rate of oogonial mitosis and second is extensive oogonial atresia. Thus, from midgestation onwards the progressive decline in germ cell number leaves only 700,000 primordial follicles at birth. This number decreases further to approximately 300,000 by the onset of puberty. Out of these only 400-500 ovulate in the entire course of reproductive life span.

This is considered an irreversible and inevitable part of female life.

Premature ovarian senescence

Approximately 10% of women suffer from premature ovarian senescence, 9% as occult primary ovarian insufficiency. In a large majority of cases POS is currently only diagnosed at advanced clinical stages when women present with clinical infertility. Risk factors for POS are known from literature and can be used to identify a sub group of young women at increased risk who are then followed sequentially with serial assessment of functional ovarian reserve until a diagnosis of POS is either reached or refuted. Approximately 25% prevalence in general US population so called mutations of fragile X mental retardation (FMR1) gene likely represents the most common known risk factor, including history based risk factors from medical, genetic, and family histories. Women so affirmatively diagnosed with POS at relative young age then have the opportunity to reconsider their reproductive planning or choose fertility preservation via oocyte or ovarian tissue cryopreservation at ages. When such procedures are clinically more effective and also cost effective.

Concept of fertility preservation for medical reasons

The concept of fertility preservation entered medical consciousness through field of oncology where increasingly successful chemo and radiation therapies have improved long term survival of young patients but often result in premature ovarian senescence. The predominant effect of cytotoxic treatments on primordial follicles in vivo is either total/ partial loss of these follicles. Chemotherapy triggers follicle activation and growth, causing burnout and depletion of ovarian reseve. The two established methods of fetility preservation are embryo and oocyte cryopreservation. Embryo cryopreservation requires patients to have a male partner or willingness of use of donor sperm as well ability to delay treatment for 2-6 weeks for stimulation and oocyte retrieval. If cancer treatment cannot be delayed some centres allow oocyte retrieval for oocyte/embryo cryoprervation soon after completing an initial round of chemotherapy. Some potential agents for cytotoxic induced ovarian damage –

GnRH analogs – suppression of pituitary gonadal axis

SIP – inhibition of sphingomyelin apoptotic patways

Imatinib – inhibition of C-ABI kinase apoptotic pathways

Tamoxifen – antioxidant, gonadal suppression

Concept of fertility preservation for social reasons

Healthy women delaying childbirth for social reasons have recently more actively been pursuing fertility preservation, motivated by concerns about inadequate functional ovarian reseve by the time they will socially be ready for conception.

Ferility prolongation for premature ovarian senescence

A large pool of patients in need of potential fertility preservation, approx 10% of women who suffer from spontaneously occurring POS have so far escaped professional attention and mostly undiagnosed progressing in their POS until becoming clinically symptomatic at advanced stages of low functional ovarian reserve. These women in large majority of cases suffer from premature ovarian aging. Age specific follicle stimulation FSH and AMH levels have been reported and allow objective determination of LFOR. Serial longitudinal investigation of FOR in young women at risk therefore allow accurate determinations whether patient deviate from normal ovarian aging or not.

Ovarian age is reflected in TOR (total ovarian reserve) of a patient. The largest part of TOR made up of still unrecruited resting primordial follicles at primitive stages of development. The early loss of ovarian reserve and subsequent menopause has major impact on fertility potential and increases risk of coronary artery disease, osteoporosis, cognitive decline and mortality later in life.

Since AMH has been suggested to play a potential role in recruitment one such gene controls the AMH type 2 receptor. Produced by granulosa cells of small growing follicles, AMH appears to inhibit recruitment as well as subsequent follicle growth. Another gene holding back recruitment is AIRE gene. When mutated it leads to rapid follicle depletion therefore POF. Mutations can lead to breakdown in self tolerance and autoimmunity.

Women on long term hormonal contraceptives who develop premature ovarian senescence at young ages therefore often go undiagnosed until termination of hormonal contraceptives, when present with either post-contraception amenorrhoea, often menstrual abnormalities or infertility. As evolving screening options now permit the detection of young women at risk for premature ovarian senescence it is proposed that young women are offered risk screening for premature ovarian senescence before starting long term hormonal contraception.

In this category of patients, what is paramount is timely detection, the possibly that can be counselled for early childbearing or oocyte preservation at an early age.

Kaplan Meier survival analysis confirmed that beta - cryptoxanthine was associated with a significant delay in onset of natural menopause. Diet containing 400 mcg of beta cryptoxanthine per day from fruits (mandarins, oranges, peaches)has significant potential to delay ovarian senescence by 1.3 yrs.

Women are increasingly delaying conception to later years.

Ovarian defects are LH dependent.

Thus GnRH antagonist treatments might provide a new noninvasive strategy for improving fertility in a subset of aging women before menopause.

Can we delay natural menopause ?

Ovarian tissue is more sensitive to aging than any other tissue in human body as it gets older both the number of follicles it houses and the quality of these follicles reduces. We are born with around 1.2 millions follicles and as we age OR (ovarian reserve) gradually decline leading to menopause around the age of 50.

Proecting follicles by natural methods

Some non specific anti aging options can be explored, with untested benefits .

1. DHEA:

DHEA is an endogenous steroid that originates from zona reticularis of adrenal cortex and from ovarian theca cells. DHEA is an essential prohormone in ovarian follicular steroidogenesis. Barad and Gleicher reported increased oocyte production after treatment with DHEA. A benefitial effect of DHEA on IVF outcome parameters was reported among women with significantly diminished ovarian reserves.

2. To raise ATP levels by increasing the intake B vitamins.

3. Oxygenation – counteract the deficiency of iron. Iron helps in making haemoglobin. To increase its efficiency vit. C is added which makes non-haeme haemoglobin more bioavailable. Castor oil packs are good to keep your blood flowing and detoxifying lymphatic system.

4. Role of Antioxidants – scavengers that travel around our body to capture reactive oxygen species, its deficiency may lead to ovarian aging. Ex. Glutathione, selenium, vit C, vit E. Found in various fruits.

5. Platelet rich plasma:

PRP is a relatively new and highly promising regenerative therapeutic application which can offer several therapeutic benefits without detrimental side effects as it is a direct product of own blood sample. PRP is highly rich in several growth factors that have a significant role in tissue regeneration. The main ones include epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), transforming growth factor beta 1 (TGF-B1), transforming growth factor beta 2 (TGF-B2), several classes of platelet-derived growth factors (PDGF), insulin like growth factor (IGF-1) and hepatocyte growth factor (HGF). These growth factors work in a collective manner in key parts of tissue regeneration such as cell growth, proliferation and differentiation in addition to improved oxygen delivery and circulation. While PRP helps with tissue regeneration via employment of growth factors, it also has the ability to do so without causing an inflammatory response through its anti-inflammatory molecules such as hepatocyte growth factor.

PRP is now currently being used for a variety of purposes including dermatological applications such as anti-aging, hair re-growth, dental applications, as well soft tissue regeneration. More recently, clinical trials and animal testing have provided substantial amount of evidence that PRP can have many beneficial effects in the field of infertility through its regenerative effects.

PRP application in ovarian soft tissue aims at cellular growth and proliferation in the ovaries. While the clinical evidence is still in its preliminary stages and the ovarian PRP application is still a very new practice, the existing evidence points to incredible outcomes in patients even in menopausal stages. While the experience with this application is still limited and it is still too soon to promise pregnancy to women who have entered menopause, PRP application does have some proven effects.

So far, the only published scientific documents has studied the effects of ovarian PRP infusion on 8 peri-menopausal women. According to the results of this study, following an ovarian PRP infusion, return of ovarian function was observed within three months.

Preventing Ovarian senescence futuristic options

1. Are there ovarian germline stem cells ?

For more than half a century, textbooks have stated that women and other female mammals are born with all the eggs, or oocytes, they will ever have. This supply gradually shrinks with age, and ovaries are incapable of producing more of these reproductive cells.

This dogma has taken a pounding in recent years, however. Starting in 2004, Ji Wu of Shanghai Jiao Tong University in China and Jonathan Tilly of Massachusetts General Hospital isolated stem cellsfrom the ovaries of mice, which could apparently divide to produce fresh oocytes. And earlier this year, Tilly announced that he has found cells with the same qualities, known as oogonial stem cells (OSCs), in the ovaries of middle-aged women.

These discoveries promised to offer new treatments for fertility, allowing women to have babies without worrying about an ageing supply of eggs. But as with all dogma-contradicting discoveries, they remained contentious.

Now, a new study from researchers at the University of Gothenburg is likely to fuel the controversy. Kui Liu and his colleagues used fluorescing proteins to identify the alleged egg-producing stem cells in the ovaries of mice, and found that the cells do not divide into oocytes. They published their results in the Proceedings of the National Academy of Sciences. Regardless of whether they represent "true" adult ovarian GSCs or dedifferentiated cells, their potential utility in the clinical realm has been proposed (80,81). It is argued that GSCs could replenish oocytes in women with diminished ovarian reserves, such as occurs in reproductive aging, and may also correct the issues related to germ cell senescence, such as increased mitochondrial dysfunction and aneuploidy (82. However, regardless of whether they are dedifferentiated cells or true ovarian GSCs, there is a long way to go before their attempted use in human fertility preservation. Specifically, further characterization of the conditions under which they are selected / develop in vivo and in vitro requires optimization, establishment of epigenetic "normalcy," and proof that they will ultimately lead to fertilizable oocytes that then undergo normal embryonic development after fertilization. Time will tell whether ovarian GSC or GSC-like cells provide any advantage over other approaches for obtaining germs cells for infertility treatment, such as through the use of induced pluripotent stem cell or embryonic stem cell technologies.

2. Novel methods of gene editing to delay ovarian senescence:

Deletion of nrip1 gene extends female mice longevity and delays cell senescence. Using age of female sexual maturation as biomarker we identified nuclear receptor interacting protein 1 (NIRp1) as a candidate gene that may regulate aeging. Nirp1 gene expression is elevated with ageing in visceral white adipose tissue and reduced after 4 mths of diet restriction.

Restriction of protein synthesis abolishes senescence festures. Mild restriction of cytoplasmic protein synthesis prevented induction of all assets of cellular senescence in normal and tumour derieved human cells. It allowed the cells to grow with no signs of senescent features in the presence of various inducers. When adult worms of nematodes of C-elegans were grown with restricted protein condition their average lifespan were significantly extended.

Conclusion

The fact that ovarian ageing is part of mammalian females is ingrained in our minds. However futuristic research points to a possiblity of extending female fertility well beyong the age of menopause. Likely candidates are discovery of ovarian germline stem cells, and gene editing to abolish ageing .

REFERENCES HAVE NOT BEEN ADDED DUE TO CONSTRAINT OF SPACE.

OHSS – Prediction & Prevention

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of assisted reproduction technology (ART). It is characterized by cystic enlargement of the ovaries and a fluid shift from the intravascular to the third space due to increased capillary permeability and ovarian neoangiogenesis.

The incidence of moderate OHSS is estimated to be between 3 and 6%, while the severe form may occur in 0.1-3% of all cycles. OHSS has been recognized in two forms:

- Early OHSS – within next few days after the ovulation triggering. It is related to an exaggerated ovarian response to gonadotrophin stimulation and HCG trigger.
- Late OHSS – 10 days after trigger, mainly related to the secretion of placental hCG.

Prediction of OHSS

Preexisting risk factors for OHSS

Risk Factor	Interpretation
1. Young age	Younger women have more risk of OHSS
2. Low body weight	Women with low BMI are at increased risk of BMI
3. Polycystic ovarian syndrome (PCOS)	PCOS women have increased ovarian reserve and hence are at increased risk of OHSS
4. History of elevated response to gonadotrophins	Previous h/o increased response (Sr. E2 > 2000 on the day of trigger & > 15 mature follicles, may have increased risk of OHSS
5. Previous history of OHSS	These women may have an increased response again leading to OHSS
6. Sr. AMH	It has the potential to become an excellent predictive tool (Values > 4ng/ml)
Absolute serum oestradiol (E2) concentrations	Previous Sr. E2 > 2000 on the day of trigger, points towards increased risk of OHSS
7. Ultrasonographic markers, such as the antral follicle count(AFC)	AFC > 15 may have an increased response, leading to OHSS

Secondary Risk Factors

1. Absolute levels or rate of increase of serum E2	Sr. E2 > 2000 on the day of trigger
2. Follicular size and number	>14 follicles with a diameter of 11mm
3. Large number of oocytes retrieved	>15 oocytes retrieved

None of these measures have been shown to be independently predictive of OHSS.

Interventions to prevent OHSS

Intervention	Recommendation	Effect of intervention	Level of evidence
1. Reducing gonadotrophin dose	Recommended	■ Stimulation is initiated with a low dose of FSH(i.e.,75IU), which is subsequently increased (i.e., 37.5IU) until an ovarian response is noted (follicle > 10mm). ■ Step-up regimen" has a lower risk of OHSS, cycle cancellation from hyperstimulation, other protocols	1b,4
2. Reducing gonadotrophin duration	Utilized as clinically appropriate	■ Mild" stimulation protocol with GnRH antagonist for late suppression has a lower risk of OHSS, multiple pregnancies and is cost effective	1b
		■ It also is less effective in terms of pregnancy rates than "long" protocols ■ In 'Mild stimulation protocols', delay administration of FSH till the mid or late follicular phase. ■ A major issue associated with this was early cycle cancellation due to premature luteinisation & lower pregnancy rates. However, the addition of GnRH antagonists has resulted in improved outcome.	1a
3. Individualized COS (iCOS)	Further research required	■ Individualizing IVF Treatment Regimens based on age, AFC, and FSH to calculate the FSH starting dose.	1b,2a
4. GnRHa as an ovulation trigger	Recommended	■ It produces a more tempered and shorter midcycle gonadotrophin surge (24-36 hours) in contrast to hCG by stimulating pituitary LH secretion hence incidence of OHSS is much lower.	1b

Intervention	Recommendation	Effect of intervention	Level of evidence
5. hCG as an ovulation trigger	Further research required	Lowest dose of hCG does not seem to reduce OHSS rates ■ A Cochrane Review, noted that it potentiated risk of OHSS (OR3.62;95%CI 1.85-7.06) and also showed no effect on live birthrate(LBR) and clinical pregnancy rate (CPR).	2a,2b,4
6. Adjuvant metformin therapy	Recommended	■ Metformin is associated with a lower risk of OHSS and increased clinical pregnancy rate ■ It inhibits secretion of vasoactive molecules (VEGF), during OI and thereby modulates vascular permeability. ■ Metformin reduced the risk of OHSS by 63% and increased clinical pregnancy rate (OR1.52;95%CI1.07- 2.15) without an effect on live birth rates. ■ Daily dose between 1000 and 2000mg at least 2 months prior to COS is recommended.	1a,4
7. Aromatase inhibitors (AI) for OI	Not recommended	■ Function by downregulating oestrogen production through inhibition of cytochrome P450enzymes. ■ Increase in pituitary secretion of FSH which promotes folliculogenesis. ■ In addition, the central negative feedback mechanisms still remain intact, which leads to the theory that it may reduce OHSS. ■ A recent Cochrane Review by Franik et al., however, failed to show any difference in OHSS.	1a
8. rhLH	Not recommended	■ Recombinant LH (rhLH) mimics the endogenous LH surge, with a half-life of 10 hours, and a shorter and/or lower LH peak. ■ A Cochrane Review by Youssef et al. however did not show any difference in the risk for severe OHSS between rhLH and urinary hCG.	1a,1b
9. hCG for luteal phase support	Not recommended	■ Progesterone significantly reduces the risk of OHSS with improved clinical pregnancy rates and livebirth rates in comparison to hCG for LPS	1a
10. Adjunct GnRHa use	Not recommended	■ GnRHa use increases the associated costs and rate of OHSS while lowering the pregnancy rates	1a

Secondary Prevention

The aim of interventions in these circumstances is to prevent progression to OHSS.

1. Coasting	Further research required	■ Gonadotrophins are withdrawn when a certain E2 concentration and/or a critical number of follicles are reached. ■ hCG trigger is subsequently delayed until E2 levels significantly decrease or plateau (less than 3days). ■ Coasting does not completely prevent OHSS ■ Is associated with a lower oocyte yield, and has no benefit in contrast to other interventions.	1a,4
Cryopreservation	Utilized as clinically appropriate	■ Cryopreservation alone does not reduce rates of OHSS. ■ With the advent of vitrification technique, recent studies have shown that cryopreservation has better pregnancy rates (32% increase) than fresh embryo transfer.	1a
		■ GnRHa followed by cryopreservation virtually eliminates OHSS	
3. Cycle cancellation	Utilized as clinically appropriate	■ Cancellation completely eliminates risk of OHSS but has a high financial and emotional burden	4

Alternative Methods of Prevention

1. Cabergoline	Recommended	■ Reduces the incidence of OHSS without an effect on pregnancy rates ■ Dopamine antagonist, prevents the excessive increase in VEGF mediated vascular permeability encountered with OHSS through its antiangiogenic properties. ■ Protective effect, however, did not extend to severe OHSS. ■ Should be commenced on the day of trigger at a dose of 0.5mg for 8days.	1a
2. Hydroxyethyl starch	Utilized as clinically appropriate	■ HES causes a decrease in OHSS without an effect on pregnancy rates ■ Cochrane Review by Youssef et al. noted that there was a statistically significant decrease in severe OHSS (OR 0.12; 95% CI 0.04-0.40) with HES use without any effect on pregnancy rates (OR1.20;95% CI0.49-2.95).	1a
3. Albumin infusion	Not recommended	■ Administered around the time of oocyte retrieval as they are theorized to prevent OHSS by binding to and deactivating vasoactive mediators of OHSS. ■ Albumin does not reduce OHSS rates and may cause lower pregnancy rates. ■ Also associated risks with anaphylaxis.	1a

Novel therapies

Intervention	Recommendation	Effect of intervention	Level of evidence
1. VasopressinV1a receptor antagonist, Relcovaptan	Further studies required	■ Reduces ovarian weight gain and multiple corpus luteum development in OHSS ■ Inhibits VEGF by modulating vasoconstriction and vascular smooth muscle proliferation.	2b
2. Aromatase inhibitor (Letrozole)	Further studies required	■ Function by downregulating oestrogen production through inhibition of cytochrome P450enzymes. ■ Increase in pituitary secretion of FSH which has a negative feedback effect and decreases estradiol levels in the body and hence the severity of OHSS. ■ May be helpful in mild to moderate OHSS.	4

Glossary for levels of evidence: 1a:systematic review and / or meta-analysis;1b: [3] one RCT; 2a: [3] 1well-designed controlled study without randomization; 2b: [3] 1 well-designed quasi experimental study; 3: [3] 1well-designed descriptive study;4:committee or expert opinions.

Conclusion

OHSS is a complication associated with COS which clinicians have no complete way of preventing at present. Through the various methods summarized, there are avenues by which its incidence can be greatly reduced.

This begins with the identification of the "high risk" woman through to the woman who is "at risk" and subsequently initiating the appropriate therapies. It is also an avenue towards which further research initiatives should be directed in a bid to strengthen the preexisting evidence base for available therapies and to develop novel techniques to aid in the prevention of OHSS.

REFERENCES HAVE NOT BEEN ADDED DUE TO CONSTRAINT OF SPACE.

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Progestogens in Infertility Practice

A recent Cochrane review has concluded that hCG improves pregnancy rate compared to placebo but yields similar results compared to progesterone. However, the risk of ovarian hyper-stimulation syndrome (OHSS) associated with hCG in stimulated IVF cycles limits its use as a luteal support. Luteal phase dynamics differ after GnRHa trigger in GnRH antagonist-treated cycles, the luteal phase being short or inadequate. Whether hCG offers a safe and effective luteal support in this group of women without the risk of OHSS given in a dose of 2000IU on the day of oocyte retrieval is yet to be fully understood.

Natural Progesterone

Micronized progesterone has been the most widely used form of luteal support. The effective routes of administration are intramuscular (i.m.), vaginal or rectal. It is now understood that bioavailability of micronized progesterone following oral administration is variable and hence, endometrial changes are inconsistent. In addition, side effects such as nausea, abdominal bloatedness, drowsiness are common with oral administration. The rectal route is rarely used.

Vaginal route of progesterone administration is widely accepted and preferred due to ease of administration and lack of side effects except for local irritation experienced by some women. It is available in both capsule and gel forms and the latter is better tolerated. Intra-vaginal administration results in a high uterine concentration of progesterone with relatively low levels in the peripheral circulation. The daily dose is 600-800 mg/day in 2-3 divided doses in capsule, although no dosage finding study has been performed; and 90 mg of gel (8%) once a day. Pregnancy rates are similar with both forms of vaginal preparations.

Progesterone 50-100 mg daily as i.m. injection is another form of luteal support. With the availability of vaginal progesterone, i.m. route is less often used than before. Pain, rash and abscess at the injection site and the need for daily visit to the clinic are important factors which preclude its routine use. Occasional occurrence of eosinophilic pneumonia has been reported with its use in otherwise healthy women. However, if vaginal route of administration is unacceptable or if there is severe local irritation, intra muscular route of administration is an effective alternative. Even though initial evidence suggested that i.m. route is superior to vaginal route, more recent evidence finds both the routes to be equally effective.

Since a normal CL secretes both E2 and progesterone, various modalities of treatment have been used in the luteal phase of IVF cycles in addition to progesterone to mimic the physiological luteal environment.

Estradiol plus Progesterone

Estradiol supplementation in the luteal phase in addition to standard progesterone support has been used in an attempt to improve IVF outcome in various situations-selectively in women with low E, levels during luteal phase or electively in all treated cycles. Transdermal E2 patches delivering a dose of 100 ug/ day or oral or vaginal E2 4-6 mg/day along with progesterone have all been used with variable results. The current evidence towards any benefit is limited to a better implantation rate noted in a single study with transdermal estrogen in addition to progesterone. Addition of E2 to progesterone support has not shown any improvement in pregnancy rate.

Progesterone with Gonadotrophin-releasing Hormone

Small bolus doses of GnRH have been used in an attempt to improve pregnancy rates in antagonist-treated cycles where GnRHa is used for ovulation trigger. The studies have involved administration of trigger. The studies have involved administration of triptorelin 0.1 mg on the day of oocyte pick-up (OPU), embryo transfer (ET) , 3 days thereafter. The initial data is suggestive of an improvement in both pregnancy and live birth rates. It is postulated that GnRHa may support the CL by stimulating the secretion of LH by pituitary gonadotroph cells by acting directly on the endometrium through the locally expressed GnRH receptors. Luteal-Phase GnRHa administration increased luteal phase serum hGC, E2 and progesterone concentrations. The beneficial effect could possibly be due to a combination of effects on the embryo and the CI.

Synthetic Progesterone

It is available as oral preparation. Most of the synthetic P are 19-nor testosterone derivatives and have androgenic properties. Although effective, these preparations are not recommended for the fear of inducing androgenic side effects on a female fetus.

However, Dydrogesterone, a stereoisomer of Progesterone has been extensively used and found safe and devoid of androgenic properties. It is available as an oral preparation. A single study from Kolkata comparing oral dydrogesterone was found equally effective. Another small study found use of dydrogesterone to have significantly higher Live Birth Rate.

Patki et al 2007 have reported a statistically significant better pregnancy rates with Dydrogesterone as compared with Vaginal progesterone.

Subsequently published Cochrane Database on Luteal phase support for assisted reproduction cycles clearly stated that Synthetic Progestogens namely Dydrogesterone showed a statiscally significant rates of increased pregnancy rates in ART.

The publication of Lotus 1 study An International Multicentric phase III Trial found that Oral dydrogesterone is non inferior to Micronized Vaginal Progesterone for luteal support in invitro fertilization. The results of this path breaking study has the potential to induce a paradigm shift for the treatment of the estimated 1.5 million women worldwide undergoing IVF each year.

Results of the recently concluded Lotus II trial comparing oral dydrogesterone with Vaginal 8% gel is eagerly awaited.

REFERENCES HAVE NOT BEEN ADDED DUE TO CONSTRAINT OF SPACE.

Master Class "ADAM" – 10th-11th February 2018, Mumbai

The **Masterclass** in **Male Infertility and Male sexual dysfunction** – a 2 day comprehensive Masterclass called **ADAM – "Advances in diagnosis and management of Male Infertility**" was held in Mumbai.

Dates: 10th and 11th February, 2018, Venue: Taj Santacruz, Mumbai.

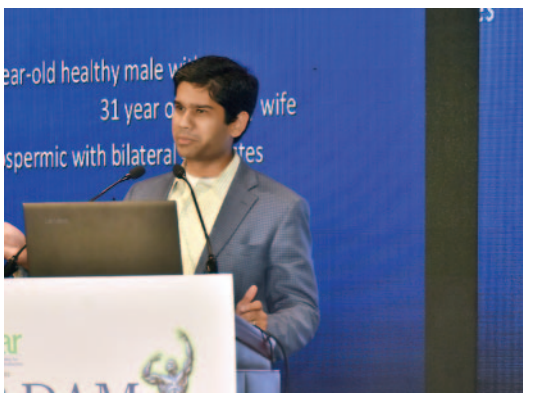
It was organized by ISAR (Indian Society for Assisted Reproduction) with scientific support from Sanofi, India.

Dr. Ranjith Ramasamy, Chief of Andrology Unit at Miami, University Florida and the doyen of Indian Andrology, Dr. Rupin Shah, were our Master Trainers and were joined by fertility experts Dr. Duru Shah, Dr. Madhuri Patil, Dr. Ameet Patki, Dr. Nayna Patel. Dr. Vineet Malhotra, a reputed Andrologist from New Delhi, also shared his expertise on the subject. Dr. Vijay Mangoli, Embryologist Mrs. Rajvi Mehta and Dr. Arundhati Athalye were also present.

The Masterclass was one of its kind and the first ever conference dealing exclusively with Andrology and targeted the Gynaecologists and Urologists alike. It was extremely well received by the delegates. About 105 delegates attended this event from all over the country, though the registration was restricted to 100 delegates only. The delegates even requested for similar Masterclass in other parts of the country.

The whole event will be archived and made available on the official website of ISAR very soon.

To conclude, **the ADAM masterclass** was an eye opener for all delegates who attended this academic feast.



ISAR Ethics Committee Guidelines Meeting – 7-8th April, Mumbai

Acknowledging the need for a few **Ehtical guidelines for ART** Practice in India, **ISAR** held a meeting on 7-8th April, 2018 in Mumbai. Dr. Duru Shah, President ISAR and Prof. Joanna Cains from Seattle, USA (International Expert on Bio-ethics) were leading the Committee.

The ISAR Ehics Committee consisted of IVF experts and was attended by Dr. Ameet Patki (Sec. Gen. ISAR), Dr. Sujata Kar (Convener, Ethics Committee meeting & clinical Secretary of ISAR), Dr. Madhuri Patil (Editor in chief, JHRS), Dr. Hitesh Bhatt (ObGyn, Legal expert), Dr. Sadhana Desai (Past President ISAR), Dr. Manohar Motwani (OBGYN), Amit Karkhanis (legal expert), Dr. Sanjay Chouhan, Dr. Anushree D. Patil (Scientists & researchers NIRRH), Ms. Subarna Ghosh (Reproductive social activist), Ms. Flavia Agnes (Lawyer and social activist).

4 Ethics Guideline were adapted from the **ASRM** and the **ICMR** Guidelines after discussions and deliberations for two days:

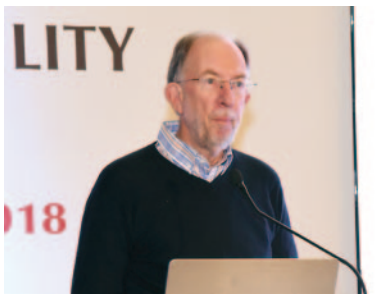
1. Guideline for fertility treatment in HIV discordant couples.
2. Guidelines for maximum number of embryos to be transferred in ART cycle.
3. Guidelines for provision of fertility services for women at increased risk of complications.
4. Guidelines for upper age limits for assisted reproductive technologies.

Master Class "PCOS & Infertility" – 24th-25th March, Mumbai

The PCOS Society of India and The Indian Society for Assisted Reproduction (ISAR) jointly organized a **Master Class** on **"PCOS and Infertility"** on 24th-25th March 2018 at Mumbai. The Master Class was an academic treat attended by nearly 100 delegates from all over India.

The distinguished speakers included both international and national faculty.

The international faculty included Prof. Robert Norman, Professor of Perciconceptual & Reproductive Medicine from the University of Adelaide, Prof. Helena Teede, President of the Androgen Excess Society and Prof. Chandrika Wijeyaratne, President of Sri Lanka Medical Association.



The national faculty included Drs. Mridubhushani Govindraj, Madhuri Patil, Sonia Malik, Sujata Kar and Duru Shah.

The program was spread over two days. The first day of the Master Class started with an Introduction by Dr. Duru Shah and Prof. Rob Norman. This was followed by interactive and educational talks on nomenclature and diagnosis of PCOS and Genotype / Phenotype in Asian versus Caucasian population by Prof. Teede and Wiyayaratne, respectively.

After lunch session included the workup and infertility management in PCOS, Genetic and environmental interplay as the etiology of PCOS and Metabolic Syndrome.

Day 2 of the Master Class started off with an exhaustive lectures on insulin resistance and ovulation induction in PCOS. Afternoon session was dedicated to Assisted Reproduction in PCOS and research methodology and collaborations.

The lectures were up-to-date, very informative and generated a lot of audience interest and interaction. The National anthems of Australia, India and Sri Lanka were played at the end of the session on the 2nd Day. The metting closed on a very happy note.

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† Schindler AE. Progestational effects of dydrogesterone in *vitro, in vivo* and on the human endometrium. *Maturitas.* 2009;65(1):S3-S11. # Data on file. ^ Novel - Estradiol hemihydrate first time in India. + Safer - As compared to conjugated equine estrogens. Smith NL *et al* Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens. *JAMA Intern MED.* 2014; 174(1):25-31.

Further information available on request: Abbott India Limited, Floor 16, Godrej BKC, Near MCA Club, BKC, Bandra (East), Mumbai 400051. www.abbott.co.in

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