Indian Society for Assisted Reproduction

THE NEWSLETTER

EXPRESS

ISSUE 3, 2021

A Woman of Substance

Lt. Dr Mehroo Dara Hansotia

2nd President of ISAR 2000 - 2003

ISAR'S Origins

BSV
bringing life to life

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Gain insights on women's reproductive health and fertility medicine with a one-stop solution to access, explore, update, interact, meet, socialize, rekindle, publish and engage.

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Each film coated tablet contains Ferrous Ascorbate IP eq to Elemental Iron 100 mg; Folic Acid IP 1500 mcg; Zinc Sulphate monohydrate IP 61.8 mg eq to elemental Zinc 22.5 mg

BLOOD HEALTH COUNTS

- Ensures rapid Hb rise[1]
- Minimal GI adverse effects[1]
- Zinc improves fetal growth[2]

50 QUALITY CHECKS

1. HERS study group; The HERS Trial report Int J Gynaecol Obstet India 2005' 8 (4): 23-303.
2. Benjamin W. Chaffee, Janet C. King Effect of Zinc Supplementation on Pregnancy and Infant Outcomes: A Systematic Review Paediatric and Perinatal Epidemiology,2012, 26 (Suppl. 1), 118–137
*IMS MAT SEP '19 PRESCRIPTION DATA

In Iron Deficiency Anaemia

Livogen®-Z

Each film coated captab contains Ferrous Fumarate IP 152 mg equivalent to 50 mg elemental iron, Folic Acid IP..750 mcg, Zinc Sulphate Monohydrate IP..61.8 mg (equivalent to elemental zinc 22.5 mg)

BLOOD HEALTH COUNTS

- Helps increase Hemoglobin levels during pregnancy[1, 2]
- Fights Iron loss due to Menstruation[3]
- Time tested highly bioavailable salt[4]

SMALL SIZE TABLET

1. Nguyen, Phuong & Grajeda, Ruben & Melgar, Paul & Marcinkevage, Jessica & Flores, Rafael & Ramakrishnan, Usha & Martorell, Reynaldo. (2012). Effect of Zinc on Efficacy of Iron Supplementation in Improving Iron and Zinc Status in Women. Journal of nutrition and metabolism. 2012. 216179. 10.1155/2012/216179. 2. Turner J, Parsi M, Badireddy M. Anemia. [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499994/
3. "Ingle, Pravinkumar. (2017). Comparative Effectiveness of Oral Iron Medications and Patient Preference in Anemia during Pregnancy" 4. Zariwala MG, Somavarapu S. Fernaud S, et al. Comparison Study of Oral Iron Preparations using a Human Intestinal Model. Sci Pharm. 2013 Jun 21;81(4):1123-39.

MAT-IN-SANG/LIV-21-000001

PRESIDENT'S MESSAGE

Dear Friends,

Over a year has passed us by since the start of the COVID-19 pandemic. A year that was filled with fears, uncertainties, rumours, myths and also hope. It brought with itself situations and events that none of us had ever experienced in our lifetimes before. All throughout there was also the light at the end of the tunnel – the much-awaited vaccine, that gave us all hope that this ordeal would end someday soon.

The vaccination drive has now started in full swing, and there is hope that the numbers should start to come down as more and more people get vaccinated. One thing has become clear that the virus is here to stay, and we need to learn to live with this new normal for a long time to come.

We have released a statement for the use of Covid 19 vaccination for sub fertile patients undergoing treatment, preconceptionally, during pregnancy and postpartum in this ISAR express issue.

We have also integrated the Life Membership process for Central ISAR and the member's respective ISAR State Chapter into one combined online registration process, the link for which can be found on the ISAR Website. The details can be found in this issue of ISAR Express.

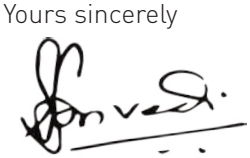
ISAR has established two funds to provide financial aid to couples struggling to conceive, especially in covid endemic time, the ISAR Dr Sadhana Desai Endowment Fund, and the ISAR Empathy Fund. You can avail of these to help your patients from lower economic strata afford the same high quality IVF services that the more affluent couples can access. Details of both these funds can be found in this issue and the disbursement is through ISAR.

As a part of the series on past ISAR Presidents that started off, this issue chronicles the life and achievements of our second President, Dr Mehroo Hansotia. This issue also has a galaxy of contributors who have written on interesting topics such as Oocyte Cryopreservation, Laparoscopic Ovarian Drilling, Management of Severe Ashermans, Use of Intrauterine Adjuvants, and Pregnancy Follow-up in Post ART Patients. We have also included an article from our pharma partners, who have always helped us by bringing in the latest technologies and drugs, and providing educational platforms, that have enriched our holistic growth.

I thank my Editorial Team for all their help and inputs, and hope you enjoy reading this issue that has been crafted with a lot of effort and care.

Wishing you all good health,

Yours sincerely



Dr. Prakash Trivedi
President ISAR 2020-2021

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GONAL-f® is the world's most prescribed r-hFSH treatment,[1,2] that has helped bring more than 4 million babies to life.[3]

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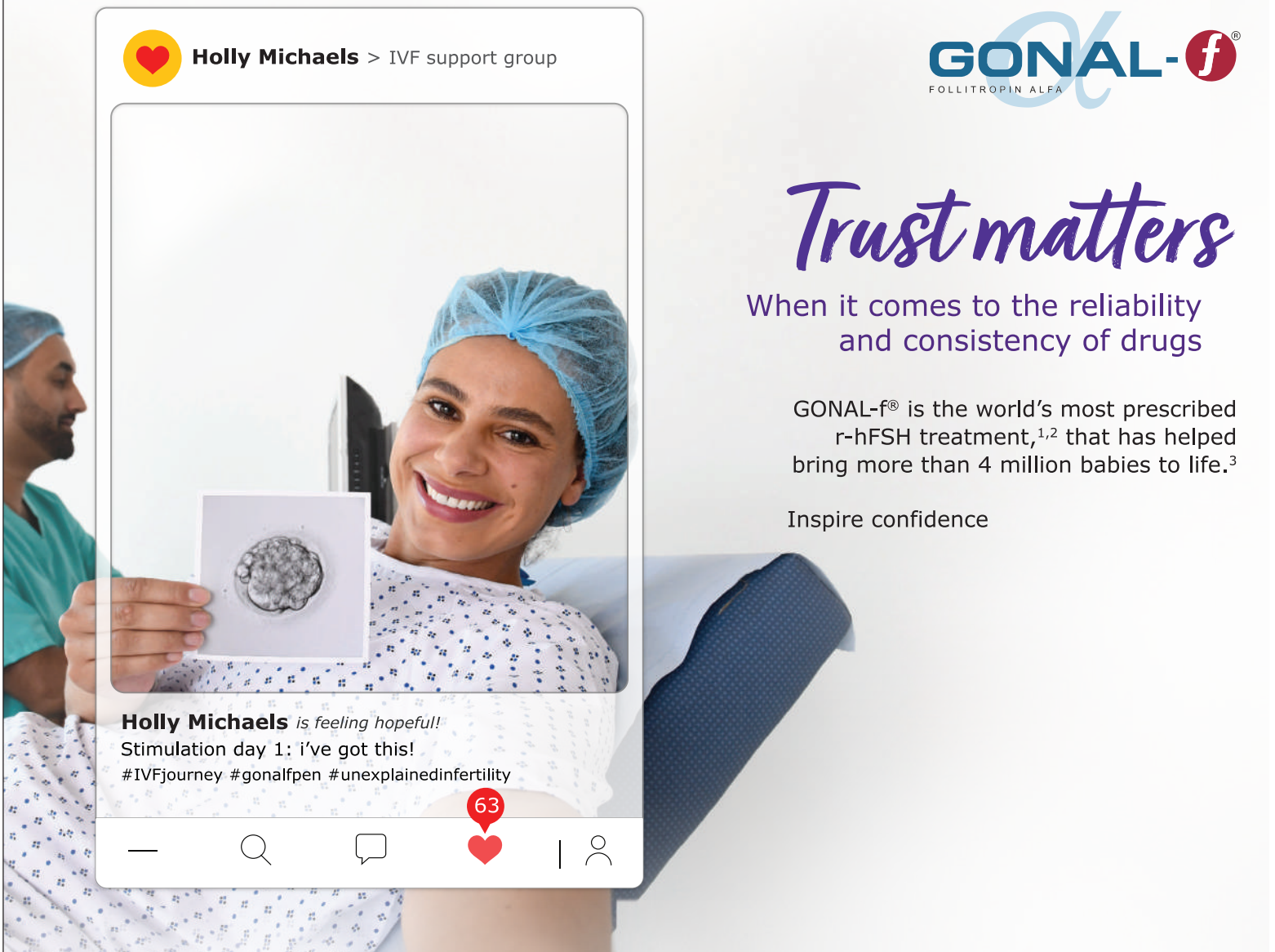

IVF: In vitro fertilization, r-hFSH: Recombinant Human Follicle Stimulating Hormone

References:

1. Data on file. IQVIA Market Data Analysis. Dec 2020. Available upon request | 2. Christianson MS, et al. J Assist Reprod Genet 2017;8:1059–1066; | 3. Longobardi S, et al. Expert Opin Drug Deliv 2019;16(9):1003 –1014.

Composition: Gonal-f 75 IU/ 450 IU/ 1050 IU: Each vial of Lyophilized powder contains Follitropin alpha I.P. 75 IU (5.5 mcg)/ 450 IU (33 mcg) / 1050 IU (77 mcg) with solvent for reconstitution. Gonal-f Pens: Each pre-filled pen contains Follitropin alpha I.P. 300 IU/ 0.5 ml (22 mcg/ 0.5 ml) / 450 IU/ 0.75 ml (33 mcg/ 0.75 ml) / 900 IU/ 1.5 ml (66 mcg/ 1.5 ml). "SCHEDULE H PRESCRIPTION DRUG – CAUTION Not to be sold by retail without the prescription of a Registered Medical Practitioner". Therapeutic indications: Gonal-f is indicated for : (i) Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomiphene citrate.(ii) Controlled ovarian hyper stimulation to induce the development of multiple follicles in medically assisted reproduction programmes (e.g. in vitro fertilization/ embryo transfer (IVF/ET), gamete intra fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI). (iii) GONAL-f in association with a luteinizing hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level <1.2 IU/L. (iv) For the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy. Dosage and administration: To be administered by subcutaneous injection. Reconstitute immediately prior to use. Up to 3 ampoules of GONAL-f may be dissolved in 1ml of solvent. Reconstitute the multidose vial with the 2ml pre-filled syringe supplied. Do not mix multidose with monodose. The dosage recommendations given for GONAL-f are those in use for urinary FSH. Women with anovulation (including Polycystic Ovarian Syndrome): GONAL-f may be given as a course of daily injections, starting by day 7 of the cycle. Treatment should be tailored to response, assessed by (i) ultrasound and/or (ii) oestrogen secretion. A common regimen starts at 75-150 IU FSH daily, increasing by 37.5 IU or 75 IU at intervals of 7 or 14 days. Maximum daily dose is usually 225 IU FSH. Abandon the cycle if response is inadequate and recommence at a higher starting dose. After an optimal response, a single injection of between 5,000-10,000 IU hCG is given 24–48 hours after the last GONAL-f injection. The patient is recommended to have coitus on the day of, and the day after, hCG administration. If response is excessive, treatment should be stopped and the hCG withheld (see Precautions). Treatment recommences in the next cycle at a lower dose. Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilization or other assisted reproduction technique: Down-regulation with a gonadotropin-releasing hormone (GnRH)-agonist is commonly used to suppress the endogenous LH surge and control tonic LH levels. GONAL-f treatment typically starts 2 weeks after the start of agonist treatment. Both are continued until an adequate follicular response is achieved. A common superovulation regimen involves administration of 150-225 IU GONAL-f daily, starting on days 2 or 3 of the cycle. The dose is adjusted according to the patient's response, to a maximum of 450 IU daily. After an adequate response, up to 10,000 IU human chorionic gonadotropin (hCG) is given 24-48 hours after the last GONAL-f injection. Men with hypogonadotropic hypogonadism: GONAL-f should be given at a dosage of 150 IU three times a week, concomitantly with hCG, for a minimum of 4 months. If after this period, the patient has not responded, the combination treatment may be continued; current clinical experience indicates that treatment for at least 18 months may be necessary to achieve spermatogenesis. Contraindications: Primary ovarian failure, malformations of sexual organs and fibroid tumours of uterus incompatible with pregnancy, ovarian enlargement or cyst of unknown aetiology, gynaecological haemorrhages of unknown cause, ovarian, uterine or mammary carcinoma, hypothalamic or pituitary tumours, prior hypersensitivity to FSH, or any excipients, or when an effective response cannot be obtained. In men, primary testicular insufficiency. Warnings and Precautions: Patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia. Patients undergoing stimulation of follicular growth, whether as treatment for anovulatory infertility or ART procedures, may experience ovarian enlargement or develop hyperstimulation. If an FSH dose increase is deemed appropriate, dose adaptation should preferably be at 7-14 day intervals and preferably with 37.5-75 IU increments. Ovarian hyperstimulation syndrome (OHSS) can develop but is minimized by careful monitoring and withholding hCG. In patients undergoing ovulation induction, the incidence of multiple pregnancy is increased compared with natural conception. The incidence of pregnancy loss by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than following natural conception. Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for infertility treatment. The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. In women with recent or ongoing thromboembolic disease or women with generally recognised risk factors for thromboembolic events, such as personal or family history, treatment with gonadotropins may further increase the risk for aggravation or occurrence of such events. Elevated endogenous FSH levels are indicative of primary testicular failure. Patients with porphyria or a family history of porphyria should be closely monitored during treatment with GONAL-f. Deterioration or a first appearance of this condition may require cessation of treatment. Pregnancy and lactation: There is no indication for use of GONAL-f during pregnancy. GONAL-f is not indicated during lactation. GONAL-f is expected to have no or negligible influence on the ability to drive and use machines. Side-effects: The most commonly reported adverse reactions are headache, ovarian cysts and local injection site reactions (e.g., pain, erythema, haematoma, swelling and/ or irritation at the site of injection). Mild or moderate ovarian hyperstimulation syndrome (OHSS) have been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Severe OHSS is uncommon. Thromboembolism may occur rarely. Mild to severe hypersensitivity reactions including anaphylactic reactions and shock, Exacerbation or aggravation of asthma, abdominal pain, abdominal distension, abdominal discomfort, nausea, vomiting, diarrhoea, ovarian cysts, Acne, Gynaecomoastia, Varicocele & Weight Gain are the other side effects. Storage: Do not store above 25 °C. Store in the original package, in order to protect from light. Do not Freeze. Shelf life: 2 years. The reconstituted solution is stable for 28 days at or below 25°C. Date of Information: June 2019 Based on CCDS Ver 4.0 dated 27th September 2016 API /GON-f (All) /Ver No 5.0 /06-2019

IN-GON-00036 EXP 07/2023

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A portable unit specifically developed to meet the demands of IVF laboratories and patient waiting rooms. Eliminates VOC's, particles, Viruses and bacteria in the air.

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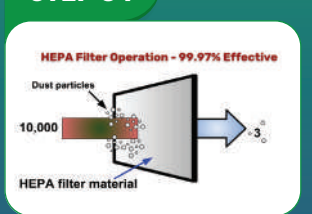
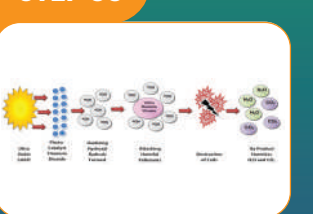


Hospital Grade High Efficiency Filter Removes Microparticles

STEP 02

Carbon Filter Adsorbs Toxic Chemicals And Gases

STEP 03



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STEP 04

Ultraviolet Light Ultraviolet light attacks the molecular structure of viruses and bacteria

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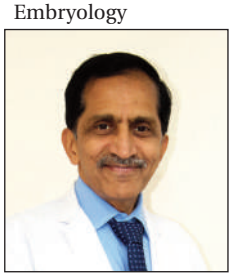

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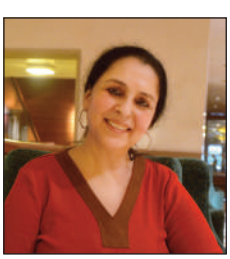

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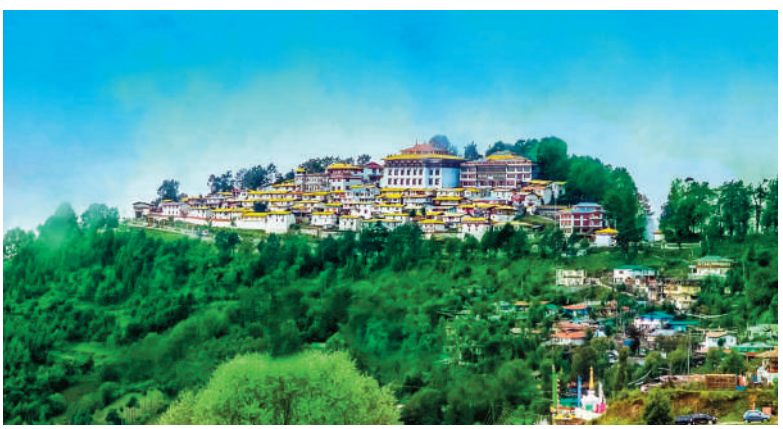

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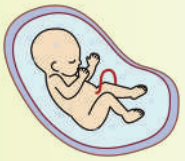
(Embryologists / ART Technologists / Counselors & Paramedical Staff)

ONLINE REGISTRATION

GREAT NEWS - YOU CAN NOW BECOME A MEMBER OF ISAR AS WELL AS YOUR ISAR STATE CHAPTER IN ONE EASY STEP BY CLICKING ON THIS LINK
https://www.isarindia.net/joinus.php

Steps for Registration:
1. Choose Type of Membership (Clinician / Embryologist / Patron Member)
2. Enter Mobile No. and Email ID, enter the OTP received.
3. Fill the Registration Form
4. Upload Documents (Qualification Certificate and State Registration Certificate)
5. Choose Payment Option (NEFT / Cheque / DD)
6. Upload passport photograph

Once the form has been successfully submitted, it will be received by the ISAR Office. On approval, an ISAR Membership No. will be auto-generated and mailed to the new member along with the Membership Certificate & online payment receipt.



DR SADHANA DESAI
ENDOWMENT FUND

FINANCIAL AID FOR UNDERPRIVILEGED INDIAN COUPLES UNDERGOING IVF / ICSI

ABOUT THE FUND
Dr Sadhana Desai established this fund to help underprivileged couples considering the exorbitant costs of IVF treatment, and ISAR graciously agreed to be part of it.

This Fund provides an aid of Rs 50,000/- per eligible couple.

Please check https://fertilityivffund.com/our-process.php to download the forms and apply for the fund.

Thank you Dr Sadhana Desai for this very benevolent gesture of helping infertile couples from all over our country by your generous contribution. **We have been lucky that one of our patients could avail treatment because of this help**. I also want to congratulate you and ISAR for making the process smooth, patient friendly & transparent.

Dr Jaideep Malhotra
ART-Rainbow IVF, Agra

We are grateful to Dr Sadhana Desai and ISAR for raising this fund to support needy couples. **We have utilised this fund's benefit to successfully treat our first patient.** Enrollment was simple. This will definitely go a long way in fulfilling the dreams of poor & needy couples in their IVF journey.

Dr Manish Banker
Nova IVF, Ahmedabad

I would like to personally thank ISAR, Dr Sadhana Desai and the fund team for such a wonderful scheme to help poor infertile couples to achieve their dreams free of cost. **It gives me immense pleasure to share this here** and appreciate their support. You are doing commendable job.

Dr Cyriac Pappachan
Lifeline Super Specialty Hospital, Adoor, Cochin, Kerala

This fund is a boon to underprivileged couples who have no option but IVF to beget their own babies. The process is unique, well designed and smoothly operated. **We are happy we could help one of our patients with it.**

Dr Anand Shinde
Deenanath Mangeshkar Hospital, Pune

Sincere thanks to ISAR & Dr Sadhana Desai for this thoughtful gesture. It's a blessing for many infertile couples who might not have ever been able to complete their families without this help. **It was easy to apply, and one of my patients has benefitted from it.**

Dr Neelam Bhise
Acme Fertility, Mumbai

ELIGIBILITY CRITERIA

1. Couple with combined annual income below Rs 5 lakh
2. Undergoing IVF or ICSI treatment in centres registered with ICMR
3. Self cycles only (couple's own eggs and own sperms)
4. For couples of Indian Nationality only

The ISAR EMPATHY FUND

FINANCIAL AID FOR COUPLES UNDERGOING IVF / ICSI

This Fund provides each eligible couple the medication required to undergo an IVF cycle

MEDICINES up to a maximum MRP of Rs 50,000/- provided (for the course of one cycle):

- Gonadotropin injections
- Antagonist injections
- Trigger injection (hCG / GnRH agonist)
- Estrogen tablets
- Progesterone supplements
- Low Molecular Weight Heparin

ELIGIBILITY CRITERIA

1. Couple with combined annual income below Rs 5 lakh
2. The treating IVF specialist should be an ISAR Member
3. Self as well as donor gamete cycles (but not for Surrogacy cycles)
4. For heterosexual couples of Indian Nationality only
5. Wife's age less than 50 years
6. The assistance will be for only one IVF treatment of a couple.

APPLICATION PROCESS

Please check https://www.isarindia.net/ISAR-empathy-fund.php for further details and to apply for the fund.
Once approved, the medicines will be issued directly to the treating centre.
The decision of selecting the patient to receive the financial aid will be at the sole discretion of the Empathy Fund Committee Members.

MARCH 2020 – APRIL 2021:

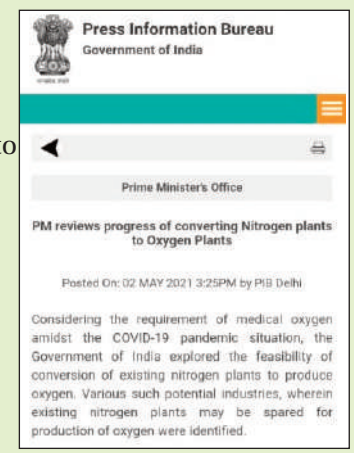
THE YEAR GONE BY

SILVER JUBILEE 25TH ANNUAL ISAR CONFERENCE
6th - 8th March, 2020 at Hyderabad. Installation of Dr Prakash Trivedi as ISAR President 2020-2021

COVID-19 PANDEMIC MEASURES

Release of the Joint ISAR-IFS-ACE Recommendations on Resuming / Opening Up ART Services During The Pandemic.
First Asian country to release such guidelines.
26th May, 2020

Liquid Nitrogen as Essential Service
Recognizing the essential nature of liquid nitrogen for the sustenance of gametes and embryos already stored at IVF centres across the country, ISAR along with IFS and FOGSI has communicated an appeal to the PM Office to reconsider the decision of converting existing nitrogen plants to oxygen manufacturing units, to ensure an uninterrupted supply of liquid nitrogen to IVF centres, without which the stored gametes and embryos cannot be sustained.


Press Information Bureau
Government of India

Prime Minister's Office

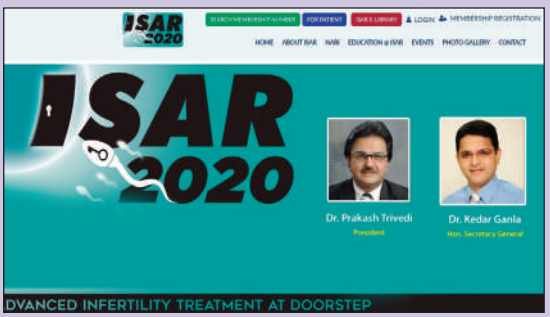
PM reviews progress of converting Nitrogen plants to Oxygen Plants

Posted On: 02 MAY 2021 3:25PM by PIB Delhi

Considering the requirement of medical oxygen amidst the COVID-19 pandemic situation, the Government of India explored the feasibility of conversion of existing nitrogen plants to produce oxygen. Various such potential industries, wherein existing nitrogen plants may be spared for production of oxygen were identified.

ISAR WEB ACTIVITIES

Revamping of ISAR Website and dividing it into a Main Section, a Patient Education Section and an ISAR E-Library.



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First ever ISAR e-Conference

29th, 30th May 2020
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All that a Clinician should know about COVID-19 and fertility in times of COVID-19
2nd May 2020
Supported by BSV & Science Integra
Attended by 1890 delegates

ISAR Abbott International Speaker Program
6th September 2020
Attended by 800 delegates

Endometriosis: Simplifying all complexities
28th April 2020
Attended by 1586 delegates

ISAR Inspire Webinar Series
2nd, 9th & 30th August 2020
Supported by Intas
Attended by 2596 delegates

Fertility Updates Webinar
With Cooper Surgical and Roche
13th August, 2020
Attended by 500 delegates

ISAR Globe-con 2020
With Cooper Surgical
16th August, 2020
Supported by Intas
With a galaxy of international speakers, this successful program was **attended by delegates from 33 countries!**

Joint webinars with ISAR and Abbott

Four webinars were conducted, and were attended by 1056 delegates in all.

Joint Webinars with ISAR and CooperSurgical

Five webinars were conducted, and were attended by 1015 delegates in all.

Joint Webinars with ISAR and Gynnext - Zydus

24 webinars were conducted, covering all aspects of reproductive medicine. Attended by over 15,000 delegates in all.

Joint Webinars with ISAR and Intermedics

Four webinars were conducted, and were attended by 1649 delegates in all.

Joint Webinars with ISAR and Emcure

Six webinars were conducted, and were attended by 3919 delegates in all.

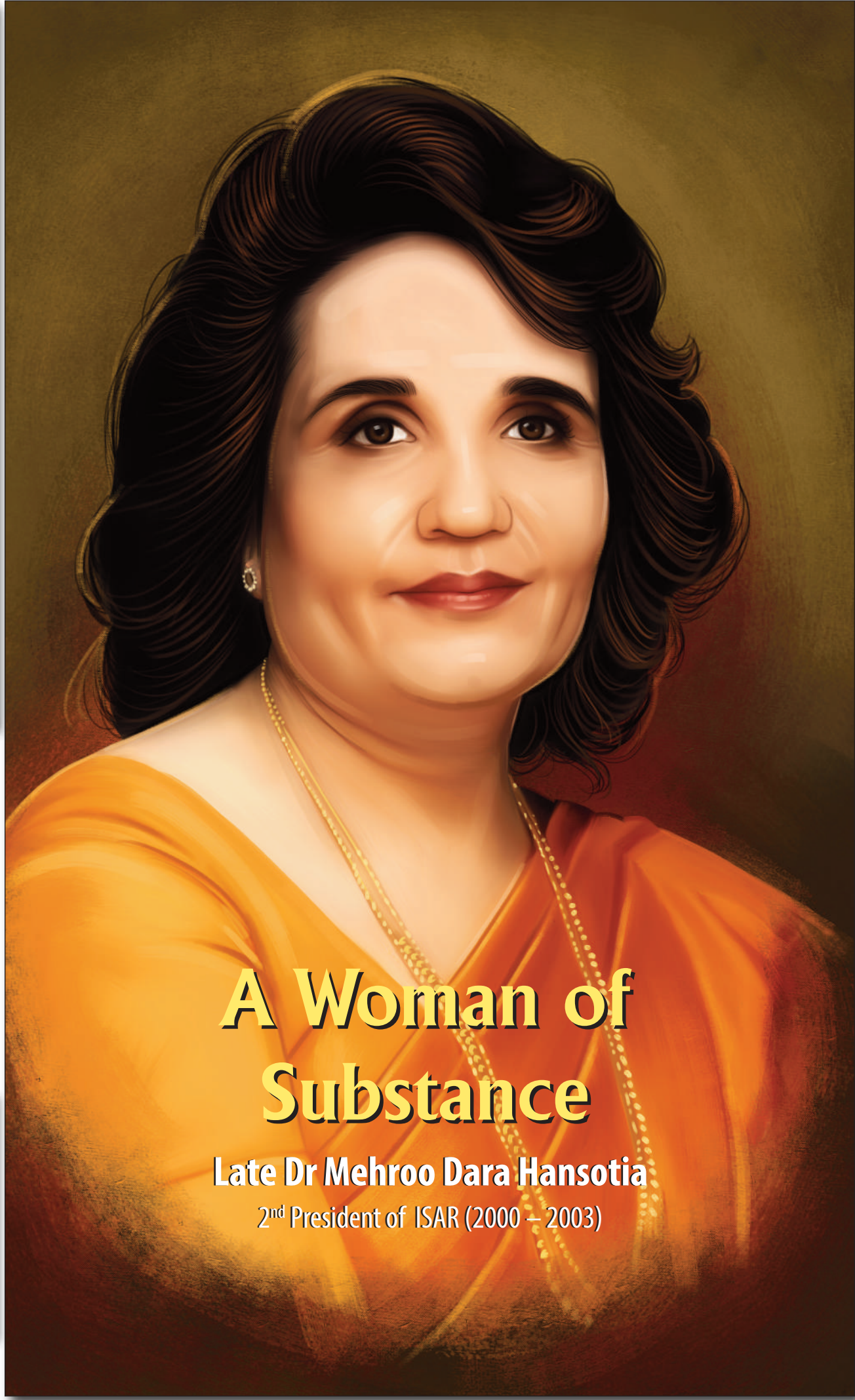
COMPILED BY

Dr Sulbha Arora

Dr Seema Pandey

Dr Ritu Hinduja

Dr Fessy Louis



A Woman of Substance

Late Dr Mehroo Dara Hansotia

2nd President of ISAR (2000 – 2003)

CONCEPTED AND EDITED

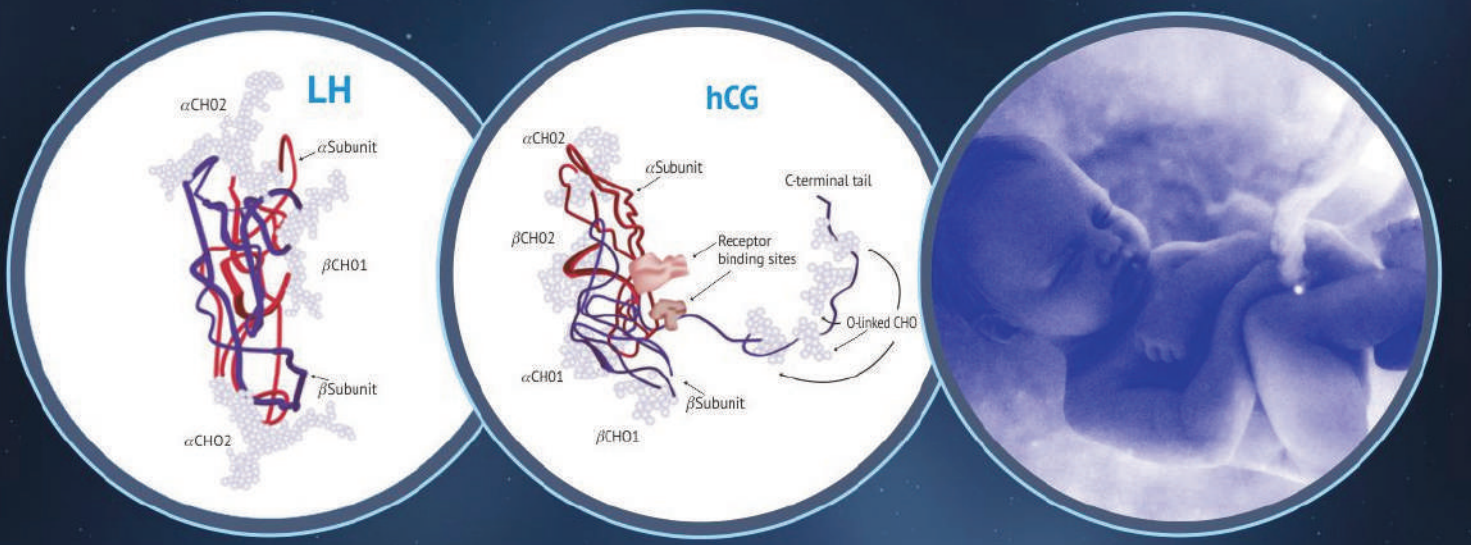
Dr Kedar Ganla

Menopur®

Menotrophin for Injection 75IU/600IU/1200IU

Driving quality with highly purified human FSH & LH[1,2]

(hCG is main contributor of LH activity)



1. **Menopur®** Prescribing Information
2. Wolfenson C et al. Batch-to-batch consistency of human-derived gonadotrophin preparations compared with recombinant preparations. Reprod Biomed Online. 2005;10(4):442-54

Menopur® [Menotrophin for Injection]

Abbreviated Prescribing Information

Composition: **Menopur®** 75 IU: One vial with powder contains highly purified menotropin (human menopausal gonadotropin, HMG) corresponding to Follicle Stimulating Hormone (FSH) activity 75 IU and luteinizing hormone (LH) activity 75 IU. Each ampoule of solvent contains 1ml Sodium Chloride solution for injection 0.9% w/v. **Menopur®** multidose 600 IU: One vial with powder contains highly purified menotropin (human menopausal gonadotropin, HMG) corresponding to Follicle Stimulating Hormone (FSH) activity 600 IU and Luteinizing Hormone (LH) activity 600 IU. One pre-filled syringe with solvent contains 1.1 ml water for injection with m-cresol. **Menopur®** multidose 1200 IU: One vial with powder contains highly purified menotropin (human menopausal gonadotropin. HMG) corresponding to Follicle Stimulating Hormone (FSH) activity 1200 IU and Luteinizing Hormone (LH) activity 1200 IU. Each of two pre-filled syringes with solvent contains 1.1 ml water for injection with m-cresol. Indications: Infertility in women caused by anovulation due to insufficient gonadotropin secretion, stimulation of follicle growth for IVF. Dosage & Administration: Dosage regimens are identical for SC and IM administration. Women with Anovulation: The recommended initial dose of **Menopur®** is 75-150 IU daily, which should be maintained for at least 7 days. Adjustments in dose should not be made more frequently than every 7 days. The recommended dose increment is 37.5 IU per adjustment, and should not exceed 75 IU. The maximum daily dose should not be higher than 225 IU. Women undergoing Controlled Ovarian Hyperstimulation for stimulation of follicle growth for IVF: In a protocol using down-regulation with a GnRH agonist, **Menopur®** therapy should start approximately 2 weeks after the start of agonist treatment. In a protocol using down-regulation with a GnRH antagonist, **Menopur®** therapy should start on day 2 or 3 of the menstrual cycle. The recommended initial dose of **Menopur®** is 150-225 IU daily for at least the first 5 days of treatment. Dose adjustment should not exceed more than 150 IU per adjustment. The maximum daily dose given should not be higher than 450 IU daily and in most cases dosing beyond 20 days is not recommended. Method of administration: **Menopur®** 75 IU is intended for subcutaneous (S.C.) or intramuscular (I.M.) injection after reconstitution with the solvent provided. The powder should be reconstituted immediately prior to use. After reconstitution with the solvent provided with **Menopur®** 600 IU and 1200 IU, it is intended for subcutaneous (S.C.) injection, as the syringe provided is for S.C. administration only. The reconstituted solution is for multiple injections and can be used for up to 28 days. Contraindications: Tumours of pituitary gland or hypothalamus; Ovarian, uterine or mammary carcinoma; pregnancy, lactation, gynaecological haemorrhage of unknown etiology; hypersensitivity to active substance or excipients; ovarian cysts or enlarged ovaries not due to polycystic ovarian disease. **Menopur®** should not be administered in patients with primary ovarian failure, malfunction of sexual organs incompatible with pregnancy, fibroid tumours of uterus incompatible with pregnancy. Warnings and Precautions: **Menopur®** should only be used by physicians who are thoroughly familiar with infertility problems and their management. Adherence to recommended **Menopur®** dosage regimen of administration and careful monitoring of therapy will minimize the incidence of Ovarian Hyperstimulation Syndrome (OHSS). Due to high risk of multiple pregnancy as compared to natural conception, patients should be advised of the potential risk prior to treatment. The prevalence of ectopic pregnancy, congenital malformations and pregnancy wastage is higher with ART as compared to normal populations. It is unclear if baseline risk of reproductive system neoplasms is increased due to treatment with gonadotropins. Women with generally recognised risk factors for thromboembolic events, such as personal or family history, severe obesity (Body Mass Index > 30 kg/m2) or thrombophilia may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotrophins. Adverse Reactions: Common (> 1/100 to < 1/10): Nausea, abdominal pain, abdominal distension, headache, injection site reactions, OHSS, Pelvic Pain. Uncommon (> 1/1,000 to < 1/100): Vomiting, abdominal discomfort, diarrhea, fatigue, dizziness, ovarian cyst, breast complaints, hot flush. Rare (> 1/10,000 to < 1/1,000): acne, rash. Unknown: Ovarian torsion, pruritis, urticaria, thromboembolism, hypersensitivity reactions, increased weight, musculoskeletal pain, pyrexia, malaise, visual disorders. The most frequently reported adverse drug reactions (ADR) during treatment with **Menopur®** in clinical trials are Ovarian Hyperstimulation Syndrome, OHSS, headache, abdominal pain, abdominal distension and injection site pain. None of these ADRs have been reported with an incidence rate of more than 5%. For more details on undesirable effects, please see package insert. Overdosage: The effects of an overdose is unknown, nevertheless one could expect ovarian hyperstimulation syndrome to occur. List of Excipients: **Menopur®** 75 IU Powder: Lactose monohydrate, polysorbate 20, sodium hydroxide, hydrochloric acid Solvent: Sodium chloride, hydrochloric acid, water for injections. **Menopur®** multidose 600 IU and 1200 IU Powder: Lactose monohydrate, polysorbate 20, sodium phosphate dibasic heptahydrate, phosphoric acid Solvent: Metacresol, water for injection Incompatibilities: **Menopur®** should not be administered in the same injection with other products, except Ferring's urofollitrophin (FSH) BRAVELLE. Storage Condition: **Menopur®** 75 IU - Do not store above 25°C. Do not freeze. Store in the original container in order to protect from light. **Menopur®** multidose 600 IU and 1200 IU - Store in a refrigerator (2°C - 8°C). Do not freeze. Shelf Life: **Menopur®** 75 IU - 2 years. For immediate and single use following reconstitution. **Menopur®** multidose 600 IU and 1200 IU - 3 years. After reconstitution, the solution may be stored for a maximum of 28 days at not more than 25°C (preferably in a refrigerator). Do not freeze. Presentation & Pack Size: **Menopur®** 75 IU: 5 vials of powder and 5 ampoules of solvent. **Menopur®** multidose 600 IU: 1 vial of powder, 1 pre-filled syringe with solvent for reconstitution, 1 needle for reconstitution, 9 disposable syringes for administration graduated in FSH/LH units with pre-fixed needles. **Menopur®** multidose 1200 IU: 1 vial of powder, 2 pre-filled syringes with solvent for reconstitution, 1 needle for reconstitution, 18 disposable syringes for administration graduated in FSH/LH units with pre-fixed needles.

SCHEDULE H PRESCRIPTION DRUG - CAUTION

Not to be sold by retail without the prescription of a Registered Medical Practitioner.

Manufactured by: **Menopur®** 75 IU - Ferring GmbH, Germany

Menopur® multidose 600 IU & **Menopur®** multidose 1200 IU - Ferring Leciva, a.s., Czech Republic.

Imported & Marketed by: Ferring Pharmaceuticals Pvt. Ltd., Thane - 421302, India

For additional information on prescribing information, kindly refer to the package insert.

Date of Revision: 7th August 2020

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Dr Mehroo Dara Hansotia

MD, FRCOG (Eng), FICS, FICOG
(06.11.1939 ~ 14.02.2009)
Second President of the Indian Society of Assisted Reproduction (2000 – 2003)

We started the Know-Your-Presidents series in the last issue of ISAR Express, with the idea of chronicling the lives, years, accomplishments and milestones of the ISAR Presidents. This article is dedicated by Team ISAR 2020-2021 to our Second ISAR President, the inspirational, warm-hearted, philanthropic woman of substance, Late Dr Mehroo Hansotia.

"If your actions inspire others to dream more, learn more, do more and become more… You are a leader." ~ John C Maxwell

When good leadership is in place in an organization, it can be felt throughout the entire organization. The foundation for the organization was laid by our visionary founder President, Dr Mahendra N Parikh. The baton was befittingly passed on by him to his successor, a woman who believed in leading from the front. Dr Mehroo Hansotia was a lady of extraordinary talent, competence and dedication, committed to maintaining the highest standards in medical practice, moral and ethical conduct.

The year 1978 marked a revolution in the field of assisted reproduction with the birth of Louis Brown, the world's first IVF baby followed by Inida's first IVF baby Durga. These early successes ignited a spark in the minds of other contemporary Indian stalwarts. Parenthood lies at the very heart of most couples' lives, which makes the grief of infertility all the harder to bear. Keeping this fact in mind, Dr Mehroo along with her then colleague Dr Sadhana Desai, established the ART Laboratory in 1985. In November 1986, their first IVF baby was born. This was India's second test tube baby, and the first from the private sector. Since then there was no turning back.

The childless couple's struggles were close to Dr Mehroo's heart. Their dreams were personal to her. For her they were not merely a female and a male factor or statistic that failed to produce any little statistics. For her, the couples who reached out to her were not merely 'patients', but human beings with real hopes and real fears. Everyone who knew her, swore by her compassion for her fellow human beings. Her desire to help those in need. To make a difference to their lives. Dr Mehroo Hansotia specialised exclusively in the care of the infertile couple.
Born on 6th November 1939, Dr Mehroo did her MBBS from Grant Medical College and her post graduation (MD in Obstetrics & Gynaecology) from the JJ Hospital, Mumbai. She went on to pursue further studies in the UK, where she completed her FICOG from the prestigious Hull Infirmary Hospital.

Her vast career over the following years included her attachment as Honorary Consultant and Professor of Obstetrics & Gynaecology at Wadia Hospital from 1976 to 1997; Visiting Obstetrician at Breach Candy Hospital, BD Petit Parsee General Hospital and Masina Hospital.

She served as the 42nd President of the Bombay Obstetrics & Gynaecological Society (1995-1996), and was a Member of the WHO Task Force on Education & Empowerment of the Adolescent Girl. Recognizing her expertise in the field, she was invited to deliver numerous orations and guest lectures at national and international conferences.

Dr Hansotia joined ISAR in the year 1991 and was chosen as its Senior Vice President . Right from the commencement of this then nascent organization, she instantly became enthusiastically engaged in its activities.In addition, she was a member of FIGO's special committee for Ethical Aspects in Human Reproduction and Women's Health. Among the many accolades she has received is a Special Award for education, research, science and technology from the Federation of Parsee Zorastrian Anjumans of India. During the 6th General Body Meeting of ISAR held on 10th February 2000 at New Delhi, Dr Hansotia was sworn in as the second President of ISAR, and continued to serve in this capacity till 2003.

ISAR president – Dr Mehroo Hansotia (2000-2003)
Executive Committee :

1) Dr Sharad Gogate – Hon Secretary General
2) Dr Feruza Parikh – Sr Vice President
3) Dr DK Tank – 2nd Vice President
4) Dr Murari Nanavati – Hon Jt Secretary
5) Dr Veerbala Parikh – Hon Librarian

6) Dr Jayashree Jhaveri – Hon Treasurer
7) Dr Nivedita Paghadiwala – Hon Jt Treasurer
8) Dr Vinod B Joshi – Hon Clinical Secretary
9) Members:
   a) Dr Manish Banker
   b) Dr Paresh Choksi
   c) Dr Sadhana Desai
   d) Dr Dhiraj Gada
   e) Dr Shreyas Padgaonkar
   f) Dr Kamini Rao
   g) Dr Duru Shah
   h) Dr Nimish Shelat
10) Co-opted Members:
   a) Dr BN Chakravarty
   b) Dr Asha Rao
   c) Mr Vijay Mangoli

The Society made great strides during these three years. It acquired its own spacious, fully equipped, staffed office premises, which was a great development. The financial health of the Society was not very satisfactory as all the funds had to be used for procuring the office premises and have a functional office.

The membership strength during Dr Hansotia's tenure grew to over 350. There was a sense of belonging with everyone wanting to contribute to the aims and objectives. This was reflected in improved attendance in conferences, offers for upcoming conferences & workshops, and many members coming forward to apply for positions in the Executive Committee.

Four grand annual conferences were conducted with excellent scientific programmes, good attendance and sizeable additions to the Society kitty:
1. 6th National Conference in 2000 at New Delhi
2. 7th National Conference in 2001 at Guwahati
3. 8th National Conference in 2002 at Ooty
4. 9th National Conference in 2003 at Indore

During Dr Hansotia's tenure, ISAR achieved the unique distinction of getting affiliated to the International Fertility Sterility Society in 2002. This was possible solely due to her hard work, as well as the timely financial support of USD 300 given by her to pay for the contribution for this affiliation. She gracefully refused the repayment by the Society, a very noble gesture indeed!

The National ART Registry of India (NARI) was set up by Dr Manish Banker on the lines of ART Registries abroad during her tenure. The Society also launched its website in the year 2002. It was a well designed site with a wealth of information for the general public, as well as for clinicians and scientists working in the field of ART. This was possible only due to Dr Hansotia's perseverance. She also found a sponsor for the website.

The Society was at the forefront in the evolution of guidelines for setting up an ART regulatory act. The National Task Force set up for this purpose consisted of President Dr Mehroo Hansotia, along with members Dr Sadhana Desai, Dr BN Chakravarty, Dr Firuza Parikh, Dr Kamini Rao, Dr Sulochana Gunasheela, Dr M Kochhar, Dr Sudarshan Ghosh-Dastidar and Dr Indira Hinduja. An ART group was set up to raise awareness in the medical community and the general public. Suggestions and reactions were sent to the concerned authorities to make the act more friendly and helpful for patients as well as ART professionals.

9th National Congress held at Indore from 14th to 16th February, 2003:
Dr Dhiraj Gada was the Organizing Chairperson. The Workshops included Male Infertility, Basics of Gynaec Endoscopy, Semenology (Semen Banking & Preparation), Pre Implantation Genetic Diagnosis, and Ultrasonography, Colour Doppler & 3D Sonography. There were 64 guest lectures delivered by national and 12 international speakers. The Congress Orations were delivered by Prof Jean Cohen (France) and Prof Stuart Campbell (UK). The key note addresses and debates were well received. There Cultural Programme was attended by over 450 people, and the Scientific Exhibition had stalls put up by 27 companies.

Most of her contemporaries and colleagues reminisce about her as a dynamic lady who made things happen. Unfortunately she had to take a backseat from the Society's activities due to her failing health and her bypass surgeries, a trying time during which her husband, her steady rock of support, Mr Dara Hansotia was constantly by her side.

MEMORIES OF DR MEHROO HANSOTIA…

By Dr Sadhana Desai

When I think of my dear friend and colleague Mehroo Hansotia, it opens the floodgate of memories as if it is yesterday once more. A lady with lot of self confidence & ambition was ready to take on the world from the word go. Both of us started our practice in the era when infertility treatment was in nascent stage. To explore & do something in this field bonded us to start the super-speciality Fertility Clinic & IVF centre as partners.

I recall our learning days and the hardships that we faced together and the joy later on giving India the first IVF baby from a private set up way back in November, 1986 within three months of India's first scientifically proved IVF baby. Sorrow, joy & frustration together we shared.

Mehroo was always immaculately dressed & had a suave manner. Inside her steely appearance she carried a soft kind soul whose generosity has been experienced by her innumerable students, colleagues and patients. Her outburst against any wrongdoing would be instantaneous but she would never harbour it in her mind.

Being a professor in Wadia maternity hospital, she was deeply involved in academic & clinical activities. She was articulate, meticulous, disciplined and had respect for other's time. Her organised conferences bore the stamp of her above qualities.

Her enthusiasm to remain abreast with the recent trends took her to many conferences abroad. MOGS, FOGSI and ISAR bear testimony of her commitment to spread the upto date knowledge and share her personal experience. She was a good orator and was bold enough to stamp her authority.

Mehroo in spite being a workaholic had a busy social life and she enjoyed it thoroughly. She never forgot to acknowledge her loving husband Dara as her pillar of strength. Her failing health shortened her life. She appeared like a comet and left behind her trail. She will be always remembered for her pioneering work in infertility & IVF in India.

By Dr Jaydeep Tank

I am delighted, happy and privileged to write about Dr Mehroo Dara Hansotia.

Delighted, because Dr Hansotia (Mehroo Aunty to me and and Menoo Aunty to my children), is someone I have known and been in awe of since I was a child. Happy, because she and Dara (Uncle) are a part of my family. Privileged, because to write about her means to write about one of the most dynamic and forward thinking leaders of our Profession, of ISAR, FOGSI and MOGS amongst other organisations and a true pioneer who blazed a trail of glory in Infertility practice when she brought, the then fledgling field of IVF, to the private sector in India along with Dr Sadhana Desai, surmounting many obstacles and against all odds. Amongst all her achievements in Infertility, her clinical acuity and counselling ability in all aspects of Ob Gyn is sometimes overlooked.

The use of her full name Mehroo Dara Hansotia in addressing her is absolutely intentional. Mehroo aunty and Dara uncle were - in the modern parlance - establishing couple goals long before the term became fashionable.

I got my start in organising conferences when Dr Hansotia was the President of MOGS. She had an uncanny sense of picking the right person for the right job and then having complete faith in the person to execute the work. She always gave credit and acknowledgement where due and was very generous with her praise and support. She was a powerful speaker, forthright in her views and watching her participate, put her points forward with conviction and clarity, and conduct meetings both scientific and in professional organisations was a learning experience.

My parents shared a very long friendship and a close bond with Mehroo Aunty and Dara uncle. Dinners at

her home with the "Journal Club" were always affairs full of bonhomie, great Parsi Bhonu and sparkling conversation. We were introduced to the celebrated Prof Paul Devroey by Dr Hansotia. This led to me and my brother Parikshit being able to attend at the CRG - UZ VUB in Brussels which formed the foundation of our understanding of IVF and its practice. The first oocyte pickup I ever saw was one she was doing in her clinic.
Full of joie de vivre Mehroo Aunty lived a full life and it is fitting that we have prizes and sessions in her name as also a community memorial hall in Navi Mumbai. Dr Mehroo Hansotia was a force of nature and she is missed dearly.

By Dr Sharad Gogate

I had proud privilege of working under Mehroo Hansotia's ISAR Presidentship. I had no personal interaction with her before, I did my PG. She had uncanny habit of putting you at ease. She had faith in her managing committee members' involvement and capacity. She led from the front but gave free hand to me as Secretary General, always open to suggestions. At the same time giving valuable guidance.
It was indeed a great learning experience to work with her.

By Dr ML Goenka

I organized 7th international congress of ISAR at Guwahati in 2001, when Dr Mehroo D Hansotia was president of ISAR. She helped me a lot in organizing this congress. Some international speakers were reluctant to come to Guwahati but she convinced them and we had best speakers of world at this conference. She also helped me in scheduling the scientific pro-

gram. She was one of the most experienced and respected IVF specialist of India. She started IVF when most IVF products (media, medicines, ET catheters, needles) were not available in India. Embryologists were mostly hired from abroad. Starting IVF in eighties was a big challenge. It was her dedication and persistence only which gave boost to IVF in India.

By Dr Asha Rao

Dr Mehroo Hansotia, Past President ISAR was a brilliant orator, academician, wonderful clinician & a kind teacher and cared very much for the education of youngsters. She always wanted the younger generation to learn new techniques the right way & progress.
My acquaintance with Dr Mehroo Hanostia started in the backdrop of ISAR. I had attended ISAR 2000 at Delhi where she called me beside her & asked me to

hold the ISAR 2002 at Coimbatore. She realized that I was hesitant and it was by her persuasion & encouragement from Dr Mahendra Parikh that I accepted this responsibility of ISAR 2002, the 8th National Congress of ISAR; this was conducted with the able leadership of Dr Mehroo Hansotia, who was the Organising Chairperson and I was the Organizing Secretary of ISAR 2002. She was a friend, guide & a motivator to me.

Dear Hansotia, that I knew was an iron lady with a golden heart. She was an inspiration to me and motivated me to organize the ISAR 2002 which turned out to be a successful scientific bonanza those days. ISAR 2002 was held between 14th- 17th February 2002. On 14th we had the Gynaec Endoscopy Workshop. On 15th we had the ART–ICSI Workshop at Rao Hospital under the guidance of Prof Hasani from Germany. On the 15th evening we had the Grand Inauguration of the congress at Ooty, followed by a Scientific Congress on 16th & 17th with 500 delegates which was an impressive number for those days. The Congress was attended by stalwarts like Prof Devroy from Brussels, who was star attraction of the congress and delivered the Oration on "Mild Stimulation in ART".

I will forever cherish the memories of Ooty ISAR 2002

& the wonderful experience of working along with the towering personality, Dr Mehroo Hansotia.

By Dr Nalini Mahajan

It is an honour to be asked to pen down a few words in memory of Dr Mehroo Hansotia, the 2nd president of ISAR and one of the pioneers of IVF in India. As an aspiring ART consultant, my first interaction with her was at conferences. I came to know her a little more closely when she entrusted me with the responsibility of holding the ISAR annual conference at Delhi. Working with her was an inspiration in itself. She was a dynamic and charismatic leader who lead by example. ART was very much in its infancy when she took over as president ISAR and during her tenure she placed great emphasis on dissemination of information, to ensure that the standard of practice in India was in keeping with international standards. She constantly updated herself and never hesitated to try something new and revolutionary. For me personally she was and will always remain a role model.

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Progesterone Gel 8.0% w/w

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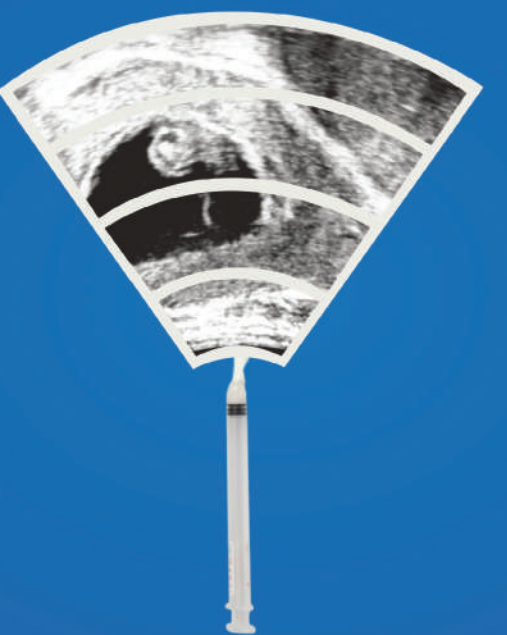

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Abbreviated Prescribing Information

Composition: Bioadhesive Vaginal Gel. Each gram contains: Progesterone IP (natural micronised): 8.0% w/w; Gel base q.s.; Each prefilled applicator delivers 1.125 gm of gel containing 90 mg of progesterone. **Indications:** Luteal Phase support in induced cycles such as In Vitro Fertilization (IVF) cycles including in oocyte donation recipient. **Dosage & Administration:** From the day of embryo transfer, 1 application of 1.125 g GESTONE™ Gel (90 mg Progesterone) should be taken intra-vaginally once or twice daily. Most women will respond to 90 mg once daily. However, some women may need 90 mg twice daily. If pregnancy occurs, treatment may continue upto 10-12 weeks. **Contraindications:** Undiagnosed Vaginal bleeding, liver dysfunction or disease, known or suspected malignancy of breast or genital organs, known or suspected Progesterone dependent neoplasia, known sensitivity to GESTONE™ Gel (Progesterone or any other ingredients), missed abortion, thrombophlebitis, thromboembolism, cerebral apoplexy or patients with history of these conditions, acute porphyria. **Warnings and Precautions:** The physician should be alert of earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). The drug should be discontinued immediately if any of these is suspected and patients carefully observed if there are risk factors for any of these conditions. Treatment should be discontinued if liver function tests become abnormal or if cholestatic jaundice appears. Drivers and users of machines should be warned about the risk of somnolence. Medicine should be kept out of reach of children. Because progestins cause some degree of fluid retention, conditions which might be influenced by this factor (epilepsy, migraine, asthma, renal or cardiac dysfunction) require careful observation. Adequate diagnostic measures to be undertaken in cases of breakthrough bleeding or undiagnosed vaginal bleeding. Patients who have a history of psychiatric depressions should be carefully observed and drug to be discontinued if depression recurs to a serious degree. Diabetic patients should be closely observed while receiving progestin therapy. **Adverse Reactions:** Common adverse events. Infections and infestations: genital candidiasis, urinary tract infections, Immune system disorders: Hypersensitivity, Nervous system disorders: Headache, migraine, dizziness, somnolence, Gastrointestinal disorders: Abdominal pain, constipation, diarrhea, nausea, vomiting, abdominal distension, Psychiatric disorders: Depression, memory impairment, aggression, nervousness, Renal and urinary disorders: enuresis, cystitis, Reproductive system and breast disorders: libido decreased, breast tenderness, breast pain, dyspareunia, pruritus, genital, vulvovaginal dryness, vaginal discharge, Musculoskelelal and connective tissue disorders: Muscle spasms, arthralgia, General disorders and administration site conditions: Fatigue, pain, Skin and subcutaneous tissue disorders: Pruritus, rash, skin disorder, urticaria. **Overdosage:** There have been no reports of overdosage with GESTONE™ Gel (Progesterone gel). In case of overdosage, patient should be observed and if necessary symptomatic/supportive measures to be instituted. **Storage:** Store in a cool place. Do not freeze. **Shelf life:** 2 years.

Presentation & Pack Size: 15 x 1 prefilled applicator containing Progesterone gel.

SCHEDULE H PRESCRIPTION DRUG - CAUTION
Not to be sold by retail without the prescription of a Registered Medical Practitioner.

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For full information on prescribing information, kindly refer to the package insert.
Date of Revision: 10th February 2021

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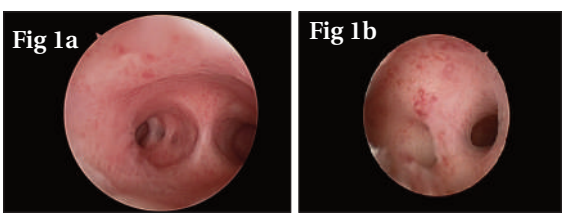
INTRAUTERINE POST SURGICAL ADHESIONS- PREVENTIVE STRATEGIES

Dr S Krishnakumar
J K Women Hospital
Nirmiti Fertility and IVF Center,
Fortis Hospital,
Mumbai

Dr Sanket Pisat
Akanksha Hospital
Nanavati, Raheja,
Holy Spirit &
Hinduja Healthcare
Hospital, Mumbai

Dr Rohan Krishnakumar
J K Women
Hospital, Mumbai

Intrauterine adhesions (IUA) involve adhesions between the opposing surfaces of the uterine cavity and occur from trauma to the basalis layer



of the endometrium-Fig 1a-1b). Heinrich Fritsch in 1894 first described the post traumatic IUA in a patient who developed secondary amenorrhea following curettage for bleeding on the 24th post partum day. Joseph G Asherman in 1948, published a series of papers on this condition, and Ashermans syndrome has been used to describe the disease ever since. Apart from oligomenorrhea to secondary amenorrhea, patients of Ashermans usually present with subfertility and recurrent pregnancy loss. D&C, especially done for obstetric reasons appeared to be a major factor behind the development of intrauterine adhesions with an overall prevalence of around 19% after a first trimester miscarriage, and the severity and incidence increase with increase in number of losses. In 4 retrospective reviews the prevalence of adhesions was 19-27%.
Following is the incidence of IUA post hysteroscopic surgeries:

Diagnostic hysteroscopy	1.6%
Septum incision	6.7%
Polypectomy	12.1%
Myoma Resection (Single)	31.3%
(Multiple)	45.5%
Hysteroscopic adhesiolysis	
(Mild- moderate)	23%
Severe)	63%

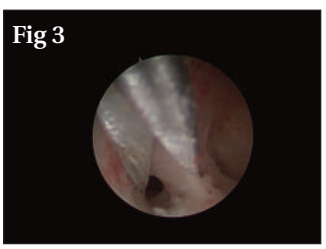
Since most of the above surgeries are done in reproductive age group, it is imperative that intrauterine adhesion formation post surgery is kept to the minimum as IUA will decrease fertility rate and also increase pregnancy complications.

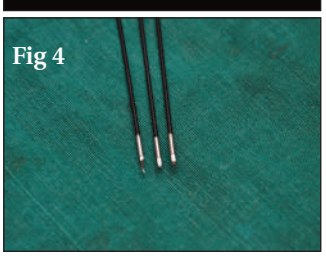
PREDISPOSING FACTORS FOR IUA POST SURGERY

1. Improper timing of surgery - Premenstrual, Post-partum, Lactation- Because of softening of the uterus, more chances of damage to the basis layer of endometrium. Hypoestrogenic state.
2. Opposing wall pathologies – Polyp / Fibroid on both anterior and posterior walls.
3. Improper surgical technique - Wrong instrumentation, Deep resection, Energy use (monopolar> bipolar).
4. Infection – Endometritis.
5. Individual predisposition - A severe form of IUA is seen in certain individuals while other undergoing the same procedure may not present similar pathology, leading to the development of a theory of individual constitutional factor or genetic factor.

PRE-OPERATIVE & OPERATIVE PREVENTIVE STEPS:

1. All hysteroscopic procedures should be done in the immediate post menstrual period.
2. Proper imaging and selection of cases - A good transvaginal sonography (2-D/3-D) to localize and map the pathology especially fibroids /polyps.
3. Diagnostic hysteroscopy - prior to operative procedure with smaller diameter hysteroscope (Fig2,2a) and sheath will help plan out the surgical procedure better, including the energy to be used. Always use hysteroscopic scissors (fig 3) for most of the pathologies excepting for fibroids. If energy is to be used prefer bipolar energy {needle (fig 4) / resectoscope (fig 5-a,5-b)} over monopolar, as damage to the endometrium could





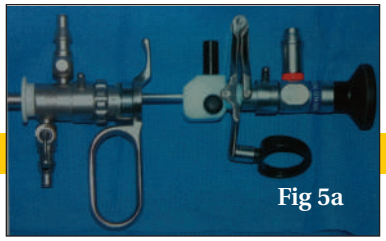


Fig 5a


Fig 5b

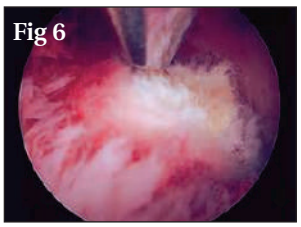


Fig 6

be more with monopolar energy. Intra uterine morcellators (Fig 6) are supposed to cause less damage to endometrium, thereby reducing IUA.

4. Counselling: Any major hysteroscopic surgery - multiple fibroids, severe Ashermans, wide large septum it is better to counsel the patient regarding a second sitting surgical procedure.

5. As a general rule literature review suggests reducing the use of electrosurgery and avoiding forceful cervical dilatation. Use of "cold loop" wherever possible for myomectomy is suggested. In a systematic review published in the European Journal of Obstetrics and Gynaecology and Reproductive Biology, Di Spiezo Sardo et al concluded that reducing the use of electric energy and reducing the damage to the healthy endometrium and myometrium is the surgical strategy to reduce postoperative IUA.

POST-OPERATIVE STRATEGIES:

The post-operative strategies to prevent IUA include: barriers (physical / gel) to separate the opposing walls and regenerate the endometrium faster. Adhesion barriers should be used in cases of severe Asherman, large, multiple fibroids, wide vascular large septum, or excessive haemorrhage during surgery.

A. Physical barriers:

a. Intrauterine Devices (IUD): IUD was the first physical barrier between the uterine walls to be used after adhesiolysis, but are no longer recommended as Lippe's loop, once considered IUD of choice after adhesiolysis is no longer available, and copper containing IUDs provoke inflammatory reaction, and also T- shaped IUDs have too small a surface area to be truly effective to act as a physical barrier. Also the risk of infection in the uterus was quantified as 8% in one series.

b. Intrauterine balloon stent : An intrauterine stent (Fig 7)) made of silicone, which because of its triangular shape conforms to the configuration of a normal uterus and maintains separation at the margins of the uterine cavity, which is where reformation is common, is placed immediately after completing adhesiolysis. In a large trial of 1240 patients treated using intrauterine stent, pregnancy rate was 61.6% and spontaneous miscarriage rate was 15.6%. An RCT comparing the efficacy of intrauterine balloon and intrauterine device in prevention of adhesions found no significant difference in the incidence and the amount of adhesion reformation between the two groups.

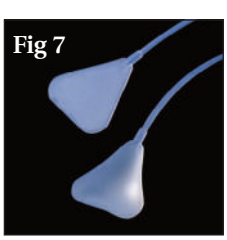


Fig 7

c. Pediatric foleys catheter: (fig 8) A no. 8 or 10 foleys with 3 ml distension of its bulb for 3-10 days after lysis of intrauterine adhesions has been reported in several studies, with good results like the balloon stent with much reduced cost. We routinely cut the tip of the catheter to fit the bulb properly close to fundus (fig 7). In a retrospective study conducted by Ru Zhu et al, it was concluded that recurrence rate of postoperative adhesions was less in ISB group than that of FB group (25%vs35.1%). The difference was seen more in severe ashermans group and was attributed mainly to the uterine cavity drainage catheter of the ISB which can drain the exudate early after the operation and reduce the formation of adhesions. The adhesion in the FB group were seen more in the periphery and top of the uterine cavity as the separation of the walls may be less with foley balloon in these areas. Use of fresh amnion graft over an inflated foley catheter, has also been used with encouraging results.

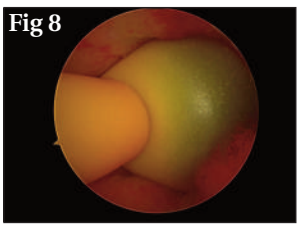


Fig 8

B. Gel barriers

Hyaluronic acid generates a temporary barrier between organs, preventing adhesion formation and is known to influence tissue repair by proliferation of mesothelial cells.

Auto-cross–linked hyaluronic acid gel (Hyalobarrier gel) (Fig 9) may be more suitable to prevent intrauterine adhesions. In a prospective RCT of 84 women, this gel was compared with no therapy after adhesiolysis. Postoperative US studies showed that the walls of the uterine cavity remained separated for at least 72 hours. At second look hysteroscopy 3 months after the surgery, intrauterine adhesions were significantly reduced in patients receiving the adhesion barrier (14%), compared with the control (32%).

Seprafilm (fig 10) A chemically modified hyaluronic acid and carboxymethylcellulose combination, has also been tried with encouraging results in several studies. A brand new hyaluronic acid (alginate carboxymethylcellulose hyaluronic acid) was evaluated in a prospective RCT including 187 cases. Four weeks after surgery, IUA were significantly lower compared with carboxymethyl cellulose hyaluronic acid.

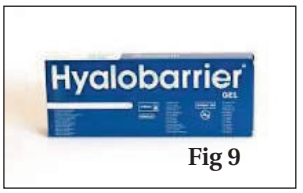


Fig 9

Oxiplex / AP Gel (Fzio Med, INC san Luis Obispo, CA) (fig11): A formulation of viscoelastic gel was shown in preclinical studies to be most effective in reducing adhesions to peritoneal surfaces following surgery. It is a new intraperitoneal gelatineous compound that is composed of polyethylene oxide and carboxy methyl cellulose stabilised by calcium chloride. Carboxy methyl cellulose decreases the injured tissue ap-

Fig 10

position required for adhesion formation. This was supported by Sardo et al who worked on 110 patients diagnosed during office hysteroscopy as having single or multiple lesions suitable for surgical treatment or resistant dysfunctional bleeding requiring endometrial ablation. These newer adhesion barrier studies provide encouraging results than traditional barriers such as IUDs, or foley catheters. Further studies are essential before these barriers are used in routine practice.

Fig 11

C. Hormone therapy:
Hormone therapy typically is given in cases where you want the endometrium to grow and epithelialize the raw surface as in cases of septal incision, Asherman adhesiolysis, and never in cases of fibroid or polyp resection. Surprisingly most studies after septoplasty have shown no benefit in terms of preventing adhesion or subsequent pregnancy rates in patients receiving adhesion barriers and hormonal treatment when compared to women undergoing septoplasty where none was used. Postoperative estrogen therapy has not been standardized in terms of dosage, duration, administration route, or combination with progesterone. In 1964, Wood and Pena described estrogen therapy to stimulate regeneration of the endometrium after IUA. Since then various regimens have been described, but no comparative studies have been performed on dosage, administration, or combination of hormones. The most popular is the use of conjugated equine estrogen in a daily dose of 2.5mg for 20 days followed by progesterone for 5 days for 2 to 3 cycles. Estradiol valerate at a dose of 4mg per day can also be used in place of Premarin. Preoperative estrogen therapy has also been suggested to be of potential benefit in increasing endometrial thickness before any surgical intervention, although data are limited.

POSTOPERATIVE ASSESSMENT:
Any surgery where post-operative rate of IUA is high, it is important to follow up these patients with assessment of the uterine cavity, usually after 2-3 cycles of treatment with either of the following;
1. Sonography: Transvaginal USG, in the mid cycle will be the best non-invasive way to look for thickness of endometrium, and for irregularity in the lining of endometrium. If Doppler is included additional information on the vascularity of the endometrium can be ascertained
2. HSG
3. Re-look Hysteroscopy (Office)
Timely recognition of any recurrence of adhesions is essential to provide the best prognosis, therefore it is necessary to repeat the surgery. Second look hysteroscopy or re-look hysteroscopy is advised in all patients desiring future fertility treatment after the following primary procedures:
1. Moderate to severe Ashermans disease
2. Multiple fibroids resection / polyp resection
3. Large broad based septum
4. Thin endometrium on transvaginal sonography in patients where a hysteroscopic surgery is done in the past.
The optimal interval for realizing the second look hysteroscopy has not been established yet. Some authors recommend very early hysteroscopy, however there is no solid evidence for such claim. According to Shokeir et al. IUAs formed immediately after the surgery are histologically different from those appearing a longer time after the operation. Early occurring IUAs are mainly composed of grade I vs. grade II/III. Indeed, early office hysteroscopy allows the lysis of newly formed adhesions, which are thin and filmy, whereas delayed adhesions are thick and fibrous and need a surgical lysis of adhesion.
In a Cochrane review (2017), on anti-adhesion therapy following operative hysteroscopy by Bosteels J, et al, which included 11 RCTs on various methods, the authors' conclusion was as follows :
Clinical effectiveness of anti-adhesion treatment for improving key reproductive outcomes or for decreasing IUAs following operative hysteroscopy in subfertile women remains uncertain and additional studies are needed to assess the effectiveness of different anti-adhesion therapies for improving reproductive outcomes in subfertile women treated by operative hysteroscopy.

TAKE HOME MESSAGE:
1. Any intrauterine surgery can lead to adhesion formation. Hence counselling of the patient for the same is to be done.
2. Proper selection of cases with proper timing and proper usage of energy has to be done. Whenever possible scissors or morcellators have to be preferred.
3. If bipolar energy is used, damage to the adjacent normal endometrium, and myometrium should be minimized.
4. Surgeries with risk factors for IUA, physical barriers like balloon or pediatric foleys catheter should be inserted, with hormonal treatment for 2-3 cycles.
5. An early (1-3 weeks after surgery) second look hysteroscopy either alone or with other preventive strategies might be useful after some types of hysteroscopic surgery where the risk of post-operative IUA is higher (eg. multiple opposing myomas). Further studies on this topic are needed.

OOCYTE CRYOPRESERVATION

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INTRODUCTION

As ART progresses, infertile couples have a chance to achieve motherhood de-spite the limitations of infertility. Oocyte cryopreservation is one of these ad-vancements in the field of ART. It is being rightly described as 'women's eman-cipation set in stone'. In a way it is a sort of fertility insurance for women who wish to delay motherhood. Cryopreservation of oocytes has yielded nu-merous successful pregnancies decades ago in USA, Europe and Australia. However, it's taken a while for it to become a regular procedure. As live birth following oocyte freezing was first reported in 1986, this technique has ex-panded its role encompassing various medical, legal and social indications. With the advent of vitrification, oocyte freezing has become more reliable as com-pared to slow freezing in terms of conception.

INDICATIONS

Oocyte cryopreservation can prove beneficial in several areas. It can be used in women suffering from cancer or premalignant conditions with promising sur-vival rates post chemo or radiotherapy. In cases, such as breast cancer, where treatment cannot be delayed, random start protocol can be used. In such cases, embryos can be created at a later stage once they find a suitable partner or they are in a remission period.

Besides malignancy, it can be used in fertility preservation in certain genetic conditions sucha s BRCA 1 and BRCA 2 mutations as these women may under-go prophylactic salpingo-oopherectomy at an early stage due to their high risk of developing ovarian cancer. Even in other genetic conditions such as Turner's syndrome, Fragile X permutation and deletion of X chromosome, oocyte freez-ing can be employed. This technology can be used even in conditions that can diminish the ovarian reserve such as severe endometriosis or Crohn's disease.

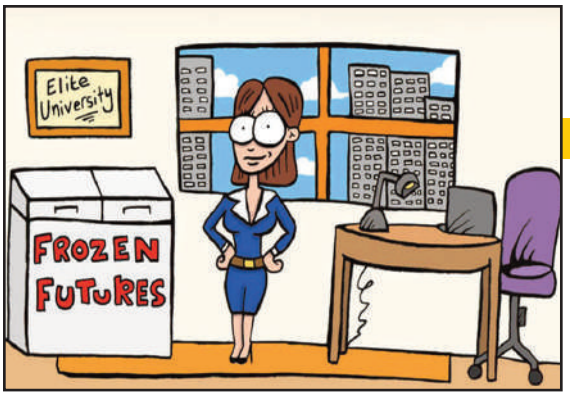
Oocyte freezing has led to donor oocyte banking which circumvents the need to match recipients' and donors' cycles. Social egg freezing has also become quite popular as awareness increases about this procedure. Women who wish to de-lay motherhood can avail of this technology. This allows women to freeze their oocytes at an early stage and create embryos when they either find a partner or are ready for parenthood.

Oocyte freezing can also be used in situations when a husband is unable to give a semen sample on the day of pick up or a failure in yielding sperms during a testicular biopsy. Another novel indication is for women with poor ovarian reserve. Pooling of oocytes and egg banking can be considered in women where multiple stimulations are required. All the collected oocytes are thawed together and ICSI is per-formed creating embryos, hence mimicking a similar situation to a normal responder. It also facilitates performing PGS as there are large a number of em-bryos. A recent indication is being developed for transgender people, who wish to undergo a sex change from female to male. There are some legal/ethical rea-sons as well for oocyte freezing. For example, in countries like Italy, as embryo freezing is not yet permitted. Oocyte freezing provides a good option and can be used later.

TECHNIQUES OF OOCYTE FREEZING

Cryopreservation refers to the cooling of cells and tissues in live condition at such low temperature, that the entire cell metabolism comes to a standstill. Slow freezing and vitrification are two techniques which have been commonly used for cryopreservation. Slow freezing (equilibrium method) is where extracellu-lar ice formation causes cellular dehydration through an equilibrium process.

Vitrification (non-equilibrium method) is a method where rapid cooling is used where high concentrations of cryoprotectants solidify without the formation of ice crystals.



The main drawback of slow freezing was its low oocyte survival rate. Evidence showed that meiotic spindle was damaged by intracellular ice formation during freezing or thawing.
Two techniques commonly used for cryopreservation are slow freezing and vitrification. Slow freezing method (equilibrium method) is a freezing method, where extracellular ice formation drives cellular dehydration through an equilibrium process. Vitrification (non-equilibrium method) on the other hand, is a form of rapid cooling which utilises very high concentrations of cryoprotectant that solidify without forming ice crystals. However, modifications in the com-bination and composition of cryoprotectants in slow freeze protocols have im-proved the survival rate of frozen MII oocytes. The technique of vitrification as a method to cryopreserve oocytes has achieved remarkable success due to its multiple advantages like being rapid, simple, inexpensive, and higher oocyte survival and pregnancy rates. In humans, most studies suggest that post-thaw survival rates of vitrified oocytes are superior to those that have undergone slow-freeze protocols.
A recent Cochrane review has also reported that Vitrification was associated with an increased clinical pregnancy rate compared to slow freezing (RR 3.86, 95% CI 1.63 to 9.11, P = 0.002). The authors concluded that Oocyte vitrification compared to slow freezing probably increases clinical pregnancy rates in wom-en undergoing assisted reproduction.

FACTORS AFFECTING SUCCESS RATE OF OOCYTE CRYOPRESERVATION

Several factors have been attributed to the success of oocyte cryopreservation. Factors, such as age, cause of infertility, stimulation protocols, number of oo-cytes, cryopreservation methods (slow-freezing and vitrification), and devices (cryotop, cryoleaf, cryotip). Age is one of the biggest factors of all the causes. A recent meta-analysis reported live-birth success rates with cryopreserved oo-cytes show an age-related decline regardless of the freezing technique used, and an aged-based probability of live birth may be calculated for cryopreserved oocytes. Another factor affecting the success is the available number of oocytes for freezing. Study by Rienzi, et al. concluded that more than eight vitri-fied oocytes are required to improve the outcome and delivery rates.

ADVANTAGES OF OOCYTE FREEZING

There are several advantages to this technique. It simplifies the oocyte donor program. It reduces the inconvenience and cost of synchronising the cycles of the donor and recipient. It also prevents loss of excess oocytes in countries where freezing of embryos is prohibited. Most importantly, it gives women control of their fertility without the worry of age and disease becoming a factor. It also al-lows cancer patients to freeze oocytes rather than the experimental ovarian tissue cryopreservation and the risk of reimplantation of malignant cells

PROBLEMS RELATED WITH OOCYTE FREEZING

There are certain concerns with this procedure as well. There could be damage to the meiotic spindle as well as cellular and sub cellular alteration which can lead to chromosomal or other cellular anomalies. However, studies are reassur-ing in this regard. Cobo., et al. showed no increase in numerical chromoso-mal abnormalities in embryos derived from oocytes slow-frozen compared with non-frozen controls.
ASRM-SART guidelines state “there is not yet sufficient statistics to recom-mend oocyte cryopreservation for the solitary purpose of circumventing re-productive aging in women because there is no data to support the efficacy, safety, ethics, emotional risks, and cost-effectiveness associated with oocyte cryopreservation for this indication”.
There is a need for long-term studies on congenital anomalies and health risk associated with egg freezing.
There is also a theoretical concern related to infectious disease due to the use of open vitrification methods. However, infectious transmission has never been observed in reproductive tissues from this technique.

CONCLUSION

Women putting their ‘eggs on ice’ have made several headlines. A recent review in 2016 summarised the history, indications, techniques, and outcomes of this technique. It stresses on ‘the real need to monitor what is being done, and the success rates achieved. It also points out that there is still a need to obtain quantitative as well as qualitative information.
Oocyte cryopreservation has provided high pregnancy and implantation rates, and thus can be considered as an efficient treatment procedure in ART. It has expanded its role from fertility preservation in cancer patients to several non-medical indications including women with risk of reduced reproductive capaci-ty owing to age-related fertility decline. Further improvements in the form of vitrification technique with successful clinical outcomes are likely to result in an increased utilisation of oocyte cryopreservation in clinical practice.

INTRA UTERINE PERFUSION OF PRP, GCSF, HCG... DO THEY HELP?

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PLATELET RICH PLASMA(PRP)

The concentrate of plasma platelets obtained by centrifugation of the patient's whole blood is PRP. Autologous PRP is derived from an individual's whole blood then centrifuged to remove red blood cells. The remaining plasma has a 5- to 10-fold higher concentration of growth factors than whole blood. These growth factors have been found to promote natural healing responses.

INDICATIONS

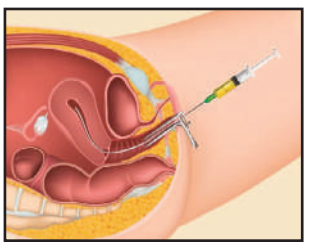
The 2 main indications for the use of PRP are for improvement of thin endometrium & recurrent implantation failure.

PREPARATION & DETAILS OF INFUSION OF PRP

PRP preparation methods involve similar procedures, such as blood collection in presence of an anticoagulant and immediate centrifugation.10 ml of the patient's blood is withdrawn from a syringe containing anticoagulant. Sequential centrifugation by soft spin of 200 × g for 15 min followed by hard spin of 600 × g for 6 min.The short, mild-spin centrifugation aims to separate the whole blood into three layers: the supernatant corresponding to the acellular plasma, the intermediate "buffy coat" containing the concentrated platelets and last, the bottom pellet rich in red blood cells. After the first centrifugation, a second faster and more prolonged spin may follow, to further isolate the "buffy coat". The volume of PRP to be infused is around 0.5 to 0.8 ml with an IUI canula or an embryo transfer catheter with all aseptic precautions. PRP is infused both in fresh and frozen thawed cycles. In fresh cycles. It can be infused on the day of hCG trigger and can be repeated after 48 to72 hrs..In FET cycles, if endometrial thickness is less than 7 mm on 12 to 13 day of estrogen primed endometrium, PRP can be repeated after 48 to 72 hrs if endometrium in not increased.

DISCUSSION OF VARIOUS SCIENTIFIC PAPERS ON PRP

Endometrial growth has been the major reported effect after PRP intrauterine administration in patients presenting thin endometrium during ART cycles. Chang and colleagues reported better endometrial growth and gestation outcomes after PRP infusion in patients with thin endometrium (< 7 mm). This first report was followed by others showing an improvement on endometrial growth and fertility treatment outcome in patients with thin endometrium. Last, a case report described the successful pregnancy outcome of a patient diagnosed with recurrent implantation failure treated with autologous PRP intrauterine administration prior to embryo transfer. Data presented on a recent report suggests that PRP intrauterine infusion promotes neo-angiogenesis. The study shows that PRP administration in infertile women undergoing frozen embryo transfer cycles with suboptimal endometrium induced a significant increase in vascularity observed by the number of vascular signals seen on Power Doppler, reaching the zones 3 and 4 of the endometrium. Endometrial thickness along with chemical and clinical gestations rates significantly increased the post-PRP treatment in this group of patients. None of these reports, however, provide any evidence on which uterine cell type (epithelial, stromal, blood, vascular, or glandular cells) and the mechanism through which the blood preparation was being effective in improving receptivity and pregnancy. There is a systematic review & metaanaysis on intrauterine infusion of autologous PRP in patient undergoing ART.The study searched databases, including Pub Med, Embase, Scopus, Web of Science, and the Cochrane Database of Clinical Trials (CENTRAL). Meta-analysis using a random-effects model was performed to calculate the pooled estimates To conclude from the above metaanalysis,intrauterine administration of PRP, irrespective of study design and study population, increases the clinical pregnancy rate in women experienced frozen-thawed ET cycle.



INTRAUTERINE INFUSION OF G-CSF

G-CSF (granulocyte colony stimulating factor) is a glycoprotein that affects cytokines and

growth factors. G-CSF boosts the endogenous cytokines secretion and enables various different endocrine routes. Receptors of G-CSF are present not only in haematopoietic lineage cells, but also in leuteinized granulosa cells, trophoblastic cells and the endometrium. In endometrium, G-CSF promotes activity of the cells and it increases blood supply.

INDICATIONS

In patients with persistent refractory thin endometrium,Recurrent implantation failures (RIF),in women with recurrent abortions & to minimize cycle cancellation rates.

METHOD OF INFUSION

Taking all aseptic precautions 300micrograms of G-CSF is pushed through IUI canula slowly and gently. IUI canula is pushed just above internal Os and G-CSF is gently infused.

TIMING OF INFUSION

G-CSF can be used both in fresh and frozen thawed cycles.In freshcycles G-CSF can be used on the day of hCG trigger and can be repeated after 48-72 hrs.
In FET cycles, if endometrial thickness is less than 7 mm on 12 to 13 day of estrogen primed endometrium, G-CSF can be repeated after 48 to 72 hrs if endometrium in not increased.

DISCUSSION OF VARIOUS SCIENTIFIC PAPERS ON G-CSF

G-CSF was first reported for use in patients with persistent thin endometrium. The first published study on the use of G-CSF in reproductive medicine was a case series in which the authors reported successful IVF outcomes after using intrauterine instillation of G-CSF in women with thin endometrium that did not respond to standard treatment (Gleicher 2011).The same authors subsequently published a larger, uncontrolled study and reported an increase in endometrial thickness after intrauterine instillation of G-CSF (Gleicher 2013). Some randomized trials were published evaluating the effectiveness of G-CSF in women undergoing IVF with chronically thin endometrium and recurrent implantation Failure (RIF) as well as in women with recurrent pregnancy loss (Scarpellini2009; Kunicki 2014; Aleyasin2016). The result of these trials varied, with some showing abenefit ofG-CSF, and others showing no improvement in outcomes (Barad 2014; Kunicki 2014; Aleyasin 2016; Kunicki 2017). A recently published systematic review evaluated the effectiveness of G-CSF in women with thin endometrium and RIF(Kamath 2017). This review suggested a possible benefit of G-CSF in women with thin endometrium and RIF undergoing IVF. Another systematic review also suggested a possible benefit of G-CSF in women with thin endometrium and RIF (Li2017).Both of these reviews conducted limited searches and suggested the need for further validation of their findings before G-CSF can be used in routine clinical practice for women undergoing IVF.

ROLE OF INTRAUTERINE HUMAN CHORIONIC GONADOTROPIN (HCG)

Human chorionic gonadotropin (hCG) is a hormone that is synthesized and released by syncytiotrophoblast and has a fundamental role in embryo implantation and early pregnancy. Endometrial advancement and luteal phase shortening due to ovarian stimulation is known. Endometrial advancement of more than three days on the day of oocyte retrieval has been associated with no clinical pregnancy in stimulated cycle. Intrauterine hCG infusion is associated with endometrial synchrony and reprogramming of stroma development following ovarian stimulation.
Intrauterine administration of hCG via IUI canula around the time of ET has been suggested to improve outcome of assisted reproduction.
Intrauterine injection of hCG before embryo transfer may increase endometrial regulatory T cells and improve the implantation and pregnancy rates.
hCG has been used in various doses (>500 IU vs < 500 IU) in different stages of embryo development like in cleavage stage and in blastocyst stage.
Method of infusion & ,indications of HCG infusion is same as that of G-CSF infusion.

SCIENTIFIC PAPERS ON USE OF G-CSF

Mansour et al., 2011,Zareietal.,2014,Santibanez et al., 2014,Pitak Laokirkkat et al.,2018, Singh R et al., 2018 found increased implantation rate after intrauterine infusion of hCG at the time of embryo transfer in fresh and frozen thawed cycle. In 2015 MaximillanSchuffetal., concluded that concluded that intrauterine administration of hCG does not improve pregnancy and life birth rates. Zhihuixuetal., 2019 investigated the effect of hCG intrauterine infusion before FET in women with endometriosis. They found good results on clinical pregnancy rates. Mara Simopoulouetal., investigated the optimal time for intrauterine hCG infusion. A total of 17 RCTs were employed. They found good results when hCG was infused 5 to 12 minutes prior to ET.

TAKE HOME MESSAGE

- Further prospective, large, and high quality randomized controlled trials (RCTs) are needed to identify the subpopulation that would most benefit from PRP.
- hCG infusion has many trails to its credit but may be still considered as controversial, meriting further RCTs to cement their true role in optimal practice.
- According to Cochrane data base there is low quality evidence to suggest that G-CSF administration may improve clinical pregnancy rate compared to no treatment or placebo in women.

PREGNANCY FOLLOW-UP IN POST ART PATIENTS

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The term 'precious baby' was first coined by Minkoff and Berkowitz (2005) for pregnancies achieved by assisted reproductive technologies (ART) and/or at an advanced maternal age and posited that such pregnancies are managed differently than others. Routinely for all ART pregnancies following embryo transfer, a quantitative serum human chorionic gonadotropin (beta-hCG) is obtained approximately 16-18 days after oocyte retrieval. All patients are then scheduled for a transvaginal ultrasound scan between 5 and 6 weeks period of gestation, to confirm intrauterine pregnancy, number, viability and to rule out ectopic implantation. Very high levels of serum beta hCG are suggestive of multiple gestation whereas very low or borderline levels may suggest non-viable intrauterine or ectopic pregnancy. Luteal phase support is usually continued up to 6-8 weeks of gestation until the luteo placental shift occurs.

WHY DO WE NEED TO BE EXTRA CAUTIOUS ABOUT ART PREGNANCIES?

First trimester bleeding in ART pregnancies

First trimester bleeding occurs in about 20% and 29-36.2% of pregnancies following spontaneous conception and ART respectively. The reason for increased incidence of first-trimester bleeding in ART is unclear. Early vanishing twins following transfer of more than one embryo may be one of the possible reasons. First trimester bleeding is associated with an increased risk for miscarriage both in spontaneous (50%) and in ART pregnancies (25%-44%). Minimal bleeding episode is associated with an increased risk for preeclampsia, preterm birth (PTB), placental abruption while in those with heavy vaginal bleeding, risk of intrauterine growth restriction (IUGR), PTB , preterm premature rupture of membranes (PPROM) and placental abruption increases. Reason postulated is chronic placental impairment due to retroplacental haematomas. Treatment is

usually conservative. Neither progesterone nor hCG injections have demonstrated to be beneficial in improving pregnancy outcome. But treatment of threatened miscarriage with progesterone compared to placebo or no treatment probably reduces the miscarriage rate (moderate quality evidence).

Early pregnancy loss in ART

The frequency of early pregnancy loss in ART is approximately 40%, similar to natural conception rate of 12-60%. Early pregnancy loss in a prior ART cycle has a positive prognostic value with no increase in biochemical pregnancy or missed miscarriage in subsequent cycles.

Ectopic and heterotopic pregnancy in ART

The incidence of ectopic pregnancies in patients conceived through ART has been reported to be 2–5% as opposed to 0.8–2 % in naturally conception. Ectopic pregnancies cases are diagnosed earlier in ART pregnancy unlike natural conception due to vigilant monitoring during early pregnancy phase. The reported incidence of heterotopic pregnancy varies from 1:100 to 1:500 in ART pregnancies and 1:30,000 in natural conceptions. Heterotopic pregnancies are diagnostic and therapeutic challenges to practitioners of ART. The presence of hyperstimulated ovaries can mask the ectopic pregnancy. In ART conception, with high levels of serum beta hCG, the clinician should make an effort to rule out any ectopic pregnancy even after documenting single intrauterine pregnancy following transfer of more than one embryo. In case of a clinical presentation of acute abdomen with documented single intrauterine pregnancy, one should rule out a heterotopic pregnancy, especially if multiple embryos have been transferred. The least invasive treatment should be used, to preserve the developing intrauterine pregnancy. The safety of laparoscopy during pregnancy has been well documented.

Late onset ovarian hyperstimulation syndrome (OHSS) in ART pregnancy

The onset of late onset OHSS is generally 12-17 days after ovulation trigger by hCG, and it is induced by endogenous hCG from the initiated pregnancy. It is usually more severe than the early onset OHSS cases. Clinical presentation varies from abdominal discomfort, gastrointestinal symptoms (e.g. nausea,vomiting and diarrhoea) to breathlessness, tachycardia and reduced urine output. Ovarian torsion and ectopic pregnancy may mimic the clinical presentation of OHSS. The hallmark imaging findings of OHSS are bilateral symmetrically enlarged ovaries containing multiple variable sized cystic lesions in ¬"spoke wheel pattern" representing enlarged follicles or corpus luteum cysts, in the presence of ascites. The laboratory investigations may suggest haemoconcentration (HCT >45%), raised leukocyte count (WBC ¬>25000/µL), electrolyte imbalance, hypoproteinaemia, deranged liver function test and kidney function test, depending upon severity of the condition. Management is usually conservative, but severe cases may require paracentesis, intravenous albumin and prophylactic anticoagulation.

Ovarian torsion in ART pregnancies

Enlarged hyperstimulated ovaries are at higher risk of ovarian torsion, reported to occur eleven times more frequently in fresh ART pregnancies than in non-ART pregnancies. The absolute incidence of ovarian torsion ranges from 0.8% in all ART cycles to 7.5% in patients with OHSS. Prompt diagnosis is essential to prevent irreversible ischemia and infarction. Most consistent ultrasound finding is unilateral asymmetric enlargement of the affected ovary.

Additionally, ovarian stromal heterogeneity and peripheral displacement of follicles may be visualized. The "whirlpool sign" - coiled vessels representing a twisted vascular pedicle - is a specific sign of torsion. A conservative approach of de-torsion in some cases can be attempted depending upon intra-operative findings. The prompt management will ensure the preservation of ovarian function without compromising pregnancy outcomes.

Prenatal screening tests in ART pregnancies

Issues complicating prenatal screening in ART pregnancies are higher maternal age and multiple pregnancy rate, vanishing twin syndrome and endocrine changes in fresh ART cycle causing alteration in the level of biomarkers for genetic diagnostic testing.(The low levels of pregnancy-associated plasma protein A (PAPP-A) in the first trimester may be due to increase in Inhibin A, which is secreted by corpora lutea. Inhibin A inhibits the secretion of PAPP-A. The mean level of free b-hCG is lower in first trimester in ART pregnancy compared with natural pregnancy. The majority of studies found no difference in the nuchal thickness (NT) between ART and non-ART pregnancies. Several earlier studies have shown that that the second trimester serum triple test markers were significantly altered among women who conceived after ART, with higher values of beta-hCG and lower values of alpha-fetoprotein and unconjugated estriol, leading to increased false-positive rates for Down's syndrome in ART. In twin pregnancy, serum levels of PAPP-A and free beta-hCG are approximately twice the concentration than in singleton pregnancies. The biochemical tests in twin pregnancies are limited by the masking effect of the normal co-twin and there is difficulty in identifying the abnormal twin. In case of vanishing twin pregnancy following ART, those who are diagnosed on early ultrasound at 8-9 weeks, can have first trimester combined screening for Down¬'s syndrome performed using the same risk calculation algorithm as in singleton ART pregnancy. In case where vanished twin is first diagnosed later in pregnancy during NT scan, it is doubtful to depend on serum markers for risk assessment. Additionally, women

pregnant after ART are less likely to take up an invasive procedure, due to 0.5–1.0% procedure-related spontaneous abortion rate associated with singleton pregnancies and twice the risk in multiple pregnancies.

Multiple pregnancies in ART
Adverse maternal and perinatal morbidities and mortalities associated with multiple pregnancies is the commonest treatment related complication of in vitro fertilisation. Nearly one in five (19.8%) deliveries in UK resulted in multiple birth. Complications of multiple pregnancy are pregnancy induced hypertension, gestational diabetes, peripartum haemorrhage, operative delivery, six fold increased risk of PTB leading to infant mortality, long term mental and physical disabilities including cerebral palsy and chronic lung disease including huge financial burden on the couple. Incidence of monozygotic pregnancy following ART is 1.6%, 2.1% after embryo biopsy while it is 0.4% following natural conception. Monozygotic twin pregnancies has higher fetal morbidities due to twin to twin transfusion, twin reversed arterial perfusion, IUGR and intrauterine fetal death.

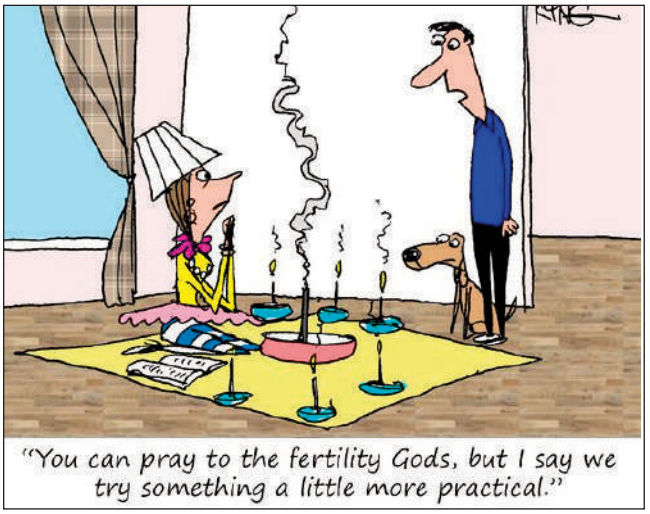
Vanishing twin in ART
The vanishing twin contributes to up to 10% of singleton births.The prevalence is higher when proportion of embryo transfers with multiple embryos is higher and directly proportional. There is higher risk of preterm delivery, low birth weight, neurological sequelae and congenital anomalies in singleton survivors of vanishing twins compared to singletons following ART conception.. This risk is mainly seen in those pregnancies where the spontaneous reduction occurred after 8 weeks of gestation. In another study, the incidence of gestational diabetes, placental abruption, premature rupture of membrane and vasa previa was found to be significantly higher in vanishing twin pregnancies compared to singleton.

Perinatal outcome in ART
Data available by systematic reviews in 2004 has shown that there was increased risk of PTB, LBW, very low birth weight (VLBW) and small for gestational age (SGA) in singleton pregnancies conceived after ART compared with those conceived after spontaneous conception. Birth defects risk increases by 30–40%. For a population with a background birth defect prevalence of 5% this equates to an absolute risk of 6.5–7.0%.

Frozen embryo transfer (FET) pregnancies
FET singletons have a higher risk of being large for gestational age (LGA) in comparison with both singletons conceived after fresh embryo transfer and the background population. Higher risk of LGA in FET singletons raises a concern due to the fact that the associated adverse outcomes such as stillbirth, asphyxia, shoulder dystocia, hypoglycemia, respiratory distress and perinatal mortality are increased in macrosomic babies.

Oocyte donation pregnancies
Oocyte donation (OD) is associated with the highest success rates among ART. Various studies have documented that OD pregnancies have an increased rate of placental disease and pregnancy-induced hypertension (PIH) due to the fact that fetus is allogeneic to the mother, exposing her to foreign antigens and cells. In OD pregnancies, the incidence of PIH ranges from 16% to 39% in singleton pregnancies and from 24.6% to 62% in twin pregnancies.

TAKE HOME POINTS
1. ART pregnancies are 'precious pregnancies' mainly because of the duration of infertility, financial, emotional and logistic issues more than the treatment itself.
2. In a woman with an ART pregnancy presenting with acute abdomen in the first trimester, additional differential diagnosis of heterotropic pregnancy, OHSS and ovarian torsion should be considered.
3. It is important to identify vanishing twin phenomenon during the first trimester ultrasound since it is more common in ART pregnancies and is associated with adverse obstetrical complications in the later half of pregnancy.
3. Biochemical tests for prenatal screening in ART pregnancy need to be carefully interpreted due to variation in levels of biochemical markers in ART pregnancies, leading to higher false positive reports. The interpretation is further complicated in presence of a vanishing twin.
4. Nuchal thickness can be used as a method of prenatal testing in ART pregnancies.
5. Careful counselling should be done before prenatal testing since women with ART pregnancies are less likely to undergo invasive prenatal testing for confirmation.
6. Pregnancies following oocyte donation are at high risk of hypertensive disoders of pregnancy and adverse perinatal outcomes even in young recipients, hence should be monitored accordingly.
7. The babies following frozen embryo transfer are associated with higher birth weight and obstetricians should anticipate issues associated with delivery of high birth weight babies.



Gujarat State Chapter Contribution

ULTRASOUND IN ASSESSMENT OF ENDOMETRIAL RECEPTIVITY

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INTRODUCTION

In the infertility management implantation is the weakest link. Implantation is dependent on the quality of the embryo and the quality of the endometrium. In spite of advancing technology in assisted reproductive technology (ART) laboratory, like time lapse camera, etc. and new studies in metabolomics, the exact quality of embryo cannot be assessed still in practice. Endometrial assessment can be done by ultrasound and ERA test.

The latter is far more expensive and invasive and therefore ultrasound is widely used for endometrial assessment in ART. Moreover, ultrasound also helps to diagnose any associated pathologies of the uterus, that may affect implantation like adenomyosis, fibroids, endometrial polyps, endometritis, etc.

Adenomyosis can be diagnosed by symmetrical/asymmetrical thickening of myometrium, with heterogenous echogenicity, irregular or interrupted junctional zone, fan shadows (alternate hypo and hyperechoic vertical strands) and altered spiral vascular pattern (figure 1). Fibroid is a well- defined round or oval, usually hypoechoic lesion, with fan and edge shadows and peripheral vascularity.(figure 2) But if it is degenerated, it may show heterogenous echogenicity and intralesional vascularity also.(figure 3). Fibroids that invade or distort the endometrial cavity (figure 4) or those that are larger than 4 cms can affect fertility. Endometrial polyps are solid echogenic lesions in the endometrial cavity, usually homogenous in echogenicity and on doppler show single feeding vessel. If these are larger than 1cms and in the upper half of the endometrial cavity, these may affect implantation. (figure 5)

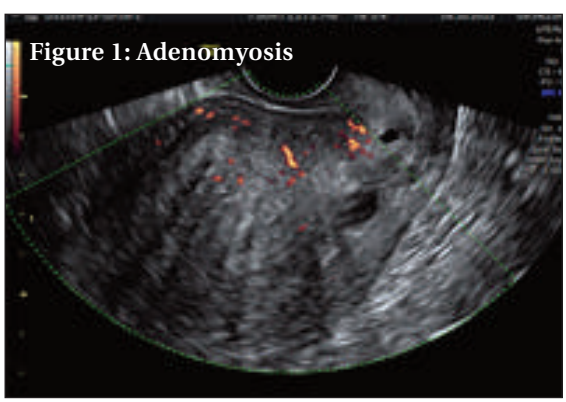

Figure 1: Adenomyosis

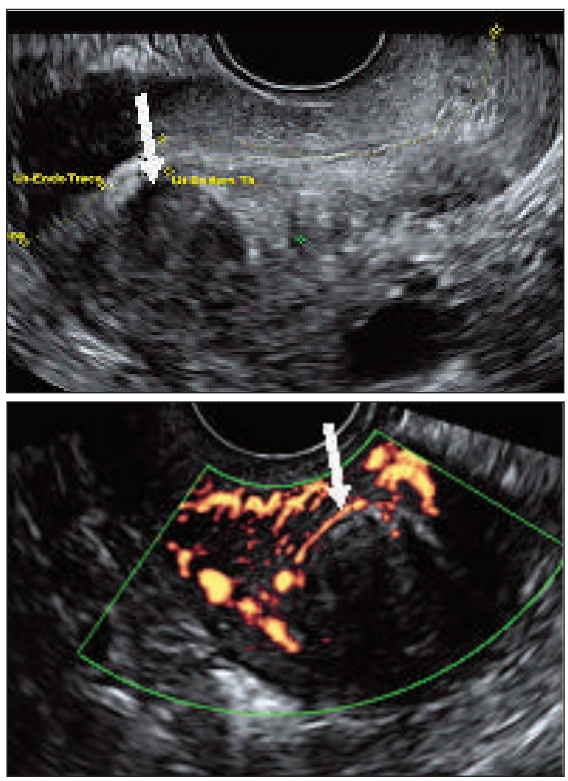

Figure 2: 2D ultrasound of fibroid and peripheral vascularity of fibroid seen on power doppler.

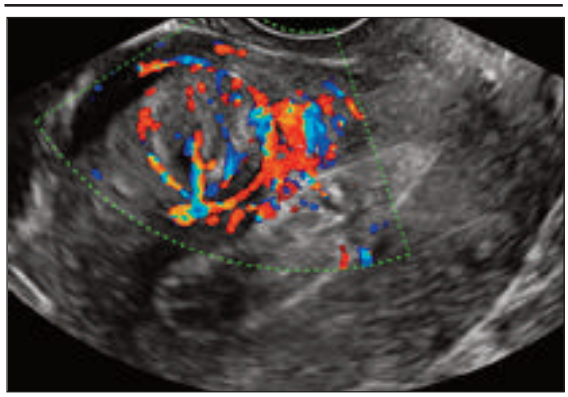

Figure 3: degenerated hyperchoic heterogenous fibroid with peripheral and intralesional vascularity

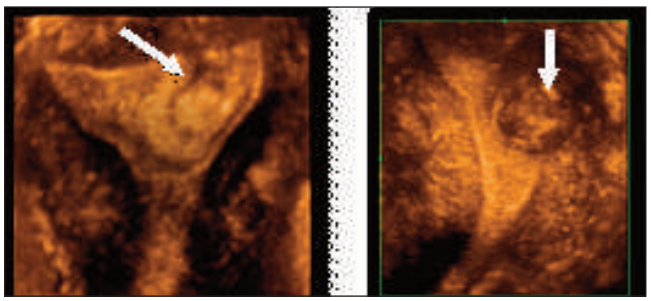

Figure 4: 3D ultrasound images of subendometrial fibroids, invading and distorting the endometrial cavity.

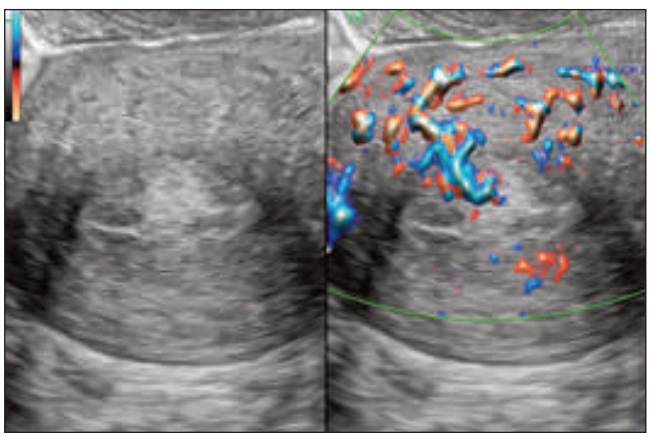

Figure 5: Endometrial polyp on 2D ultrasound and with HD low showing single feeding vessel

Its assessment by 2D ultrasound is highly popular, but that includes only the thickness of the endometrium and at the most the morphology(triple line or five line or multilayer pattern). But endometrial assessment is much more than this. Endometrium is a receptor organ for majority of the hormones involved in fertility and therefore study of its morphology and vascularity is thought to explain the mysteries of implantation failure.

B MODE FEATURES OF ENDOMETRIUM WITH GOOD RECEPTIVITY:

Endometrium starts becoming multilayer as early as 6-7 days before ovulation and after the follicle reaches 11-12 mm, the endometrium also grows at a rate of 1-2 mm per day in thickness in mid proliferative phase and 0.5mm per day in late proliferative phase. Though the endometrial dynamics is different in clomiphene citrate cycles, where endometrial thickness suddenly increases by 2-3mm or more in the later proliferative phase. Endometrial dynamicity is important. On TVS an endometrial thickness of minimum 6 mm is required on the day of trigger in intrauterine insemination or fresh transfer IVF cycles , but 8-10 mm is optimum. Very low implantation rate has been documented below 6mm of endometrial thickness. Maximum endometrial thickness that may be considered suitable for implantation is 15mm, but it is essential that even when the endometrium is too thick, it has a normal morphology.

In frozen transfer cycles it is recommended to allow the endometrium to grow to at least 8mm before Progesterone is started. The endometrial thickness is measured in true mid sagittal plane of the uterus, when the entire endometrial cavity and the cervical canal are seen in continuity. Endometrial thickness is measured from outer margin of the hyperechoic line of the endometrium to outer margin of the hyperechoic line of the endometrium, perpendicular to the central line of endometrium at the broadest part of the endometrium.(figure 6) If there is fluid in the endometrial cavity, the thickness of two lips of endometrium is separately measured and then added.

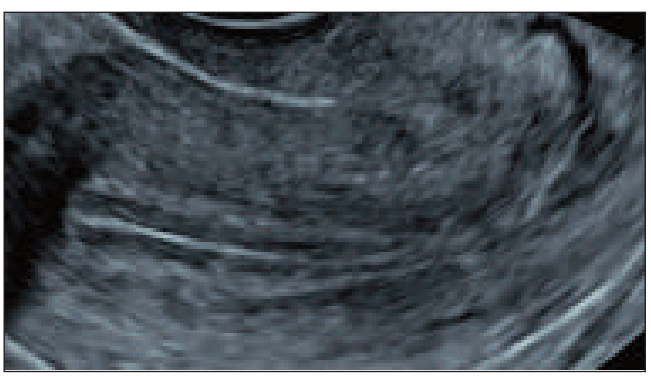

Figure 6: measuring endometrial thickness on 2D ultrasound

In all the healthy endometria, the endometrio- myometrial interface should be intact.(figure 7). Breach or irregularity of endometrio-myometrial junction is an indication of unhealthy endometrium and therefore poor receptivity.

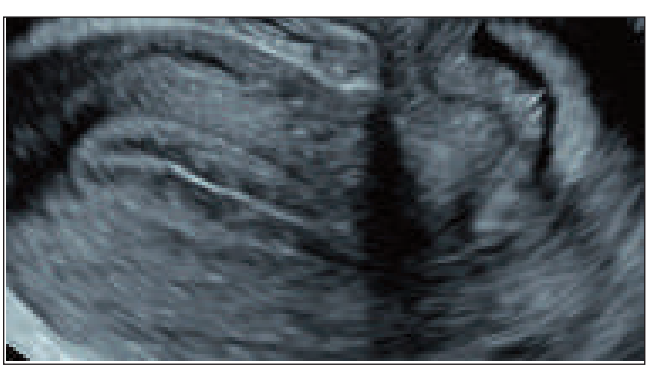

Figure 7: mid sagittal plane of the uterus on 2D ultrasound with arrow heads pointing towards thin hypoechoic line outside the endometrium-endometrio-myometrial junction.

Popularly multilayered endometrium is considered as a desired endometrial pattern. Morphologically the endometrium is graded as the best grade A, when endometrium is multilayered with the intervening area is as echogenic as the anterior myometrium. (figure 8). Endometrium is graded as intermediate or grade B(figure 9) when it is multilayered or triple line with almost anechoic intervening area. In Grade C, endometrium is homogenous and isoechoic1. (figure 10). It was thought that implantation rates may be affected by difference in morphology, but several reports by different groups2 agree on the fact that implantation rates can be more correlated to the vascularity of the endometrium rather than the thickness and morphology of the endometrium. The morphology though can be more related to the estradiol levels. With rising estradiol levels the endometrial morphology moves from grade B to grade A and then grade C. If the endometrium starts becoming hyperechoic to the myometrium, then it indicates progesterone exposure and poor receptivity.

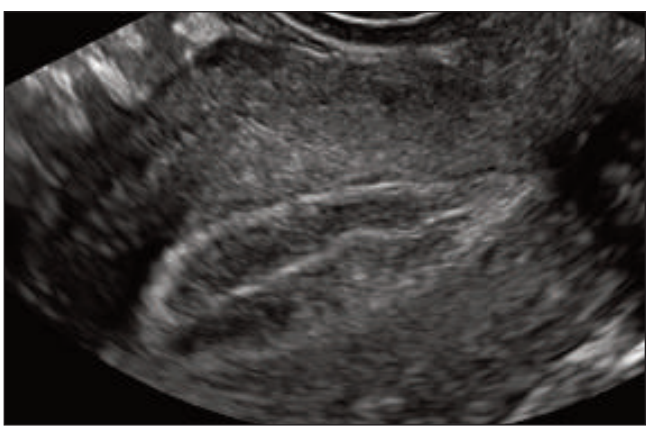

Figure 8: B mode ultrasound image of grade A endometrium.

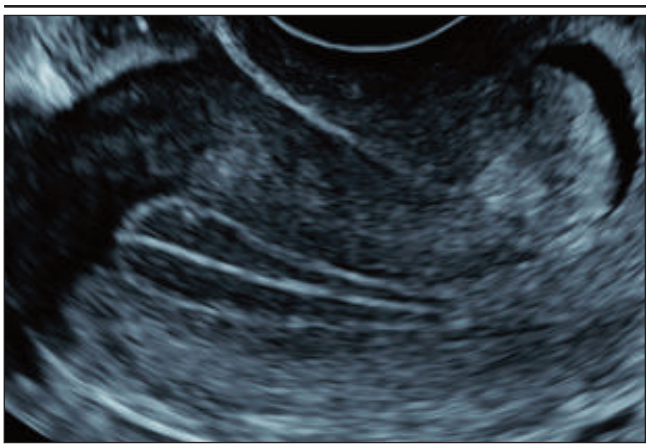

Figure 9: B mode ultrasound image of grade B endometrium

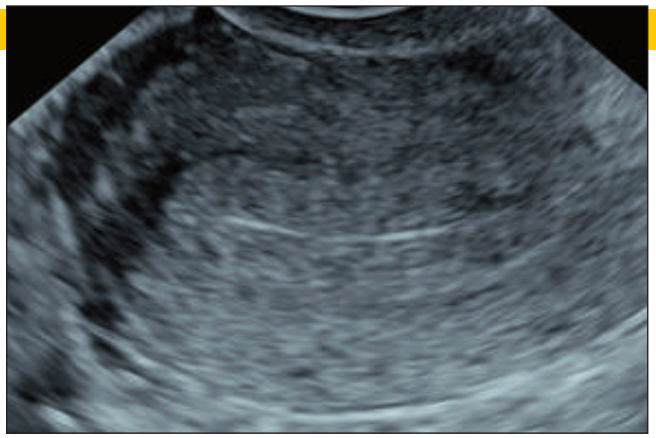

Figure 10: B mode ultrasound image of grade A endometrium.

Endometrial peristalsis is also considered one of the important parameters to decide endometrial receptivity, especially if only 2D assessment of the endometrium is done. Endometrial peristalsis in this phase of the menstrual cycle should be cervico-fundal in direction. Three to five peristaltic waves in 2 minutes of observation time may be considered as normal. If the rate is more than 5, it is considered a hyperactive endometrium, that may not be pacified enough after progesterone to allow implantation. It the rate is less than 3 then it is considered too inactive endometrium to allow sperm transfer that is essential for fertilization.

DOPPLER FEATURES OF ENDOMETRIUM WITH GOOD RECEPTIVITY:

Segmental uterine artery perfusion demonstrates significant correlation with hormonal and histological markers of uterine receptivity, reaching the highest sensitivity for subendometrial blood flow. On colour Doppler the endometrium which is mature shows vascularity in zone 3 and 4 .(figure 11) .

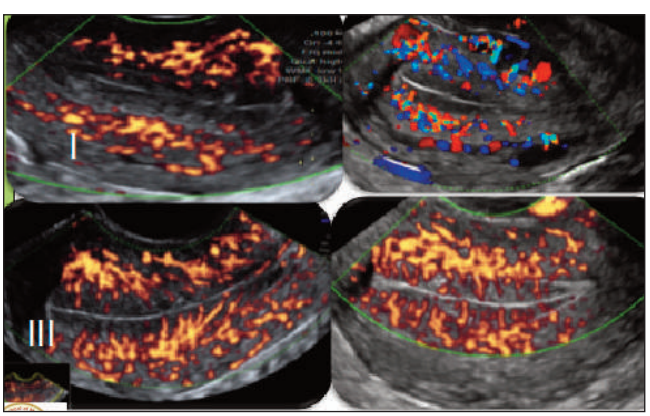

Figure 11: Power Doppler images of the grade 1-4 endometrial vascularity

The zones of vascularity are defined according to Applebaum as :

Zone 1 when the vascularity on power Doppler is seen

only at endometriomyometrial junction,
Zone 2 when vessels penetrate through the hyperechogenic endometrial edge,
Zone 3 when these reach intervening hypoechogenic zone and
Zone 4 when these reach the endometrial cavity.

ENDOMETRIAL VASCULARITY: ITS RELATION TO IMPLANTATION RATES

• Vascularity in	**Zone 1**	**Zone 2**	**Zone 3**	**Zone 4**
• % of patients	6.69%	20.73%	58%	14.47%
• + βhCG	19%	21.87%	39.77%	70.14
• Gest. sac	9.6%	14.58%	36.8%	68.65%
• abortions	50%	23.8%	5.6%	1.5%

Zaidi *et al* found that absence of flow in the endometrial and subendometrial zones on day of hCG indicate total failure of implantation.
On pulse Doppler of these arteries should have an RI of < 0.6 and should cover 5mm2 area of the endometrium, for the endometrium to be called mature for implantation .
Moreover uterine artery PI should be < 3.2 (figure 12).

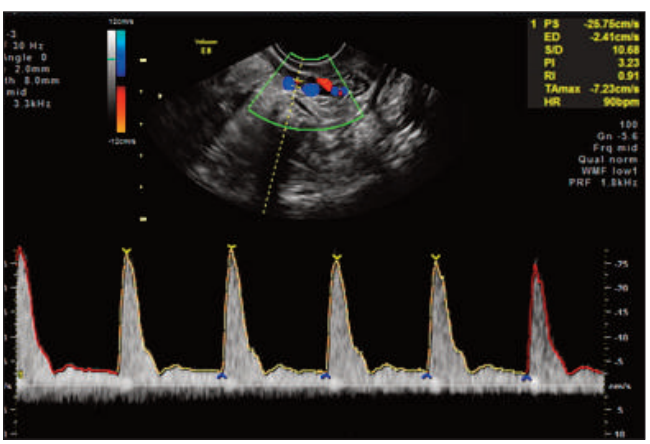

Figure 12: Pulse Doppler image showing high resistance uterine artery flow waveform.

Several authors have shown that the optimum uterine receptivity was obtained when average pulsatility index of the uterine artery was between 2 and 3 on the day of transfer or on the day of hCG5.
In such cases therefore in IUI cycles, ovulation trigger is withhold or postponed and in IVF cycles, embryos are frozen for transfer in subsequent cycles.
All these put together, almost meet all the criteria included in the popular Applebaum scoring. Endometrial thickness, multilayered endometrium, dynamicity of the endometrium, peristalsis and endometrial flow. Homogenous myometrial echogenicity and normal flow in myometrium relate to normal myometrium which indirectly can be evaluated by intact endometrial myometrial junction as it confirms absence of adenomyosis. It is important to make a note here that this Applebaum score though became very popular earlier, it is not being used as popularly now because even the full score does not relate with pregnancy always.

3D ULTRASOUND FOR ASSESSMENT OF ENDOMETRIAL RECEPTIVITY:
Lately endometrial volume is considered to be a more reliable parameter than endometrial thickness. Endometrial volume can be reliably calculated on 3D US by VOCAL (virtual organ computer aided analysis). Volume calculation of the endometrium may help to correlate the cycle outcome with quantitative parameter rather than endometrial thickness.
A study by Raga *et al* shows pregnancy and implantation rates were significantly lower when endometrial volume < 2ml, while no pregnancy was achieved when endometrial volume was < 1ml. 3D power doppler ultrasound can also be used for better assessment of endometrial vascularity. Several publication have endorsed that better endometrial vascularity improves the chance of implantation. A study by Kupesic *et al* shows lower resistance index of 0.49 – 0.57 in subendometrial vessels and FI of 11.0 – 15.4 as compared to 9.5 – 13.3 otherwise.
But it is also important to remember that endometrial vascularity studies must be done before the trigger because once LH surge starts there is decrease in vascularity for 4-5 days, till progesterone comes to a plateau. So if the vascularity pf the endometrium is assessed on day 3 transfer day, vascularity will be low, but of done on day 5, blastocyst transfer day, it is better.

TO SUMMARIZE:

Ultrasound signs of good endometrial receptivity	
thickness	8-10mm
morphology	Grade A/B
vascularity	Zone 3-4
RI	< 0.5
PSV	Preferably >3cms/s
Uterine artery	PI < 3.2
volume	At least 2 not more than7cc
3D morphology	Intact endo-myo junction
3D PD	Higher the better.

TO CONCLUDE:
Ultrasound is an excellent tool for assessment of the endometrial receptivity. Hormonal changes occurring day to day during the menstrual cycle reflects as morphological and vascular changes in the endometrium. Assessing these changes by transvaginal ultrasound and Doppler and correctly interpreting these, can reliably assess endometrial receptivity and is highly cost effective and patient and clinician friendly. Since it also can be used to diagnose associated abnormalities of the uterus that affect implantation potential of the endometrium.

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PELVIC INFLAMMATORY DISEASE

OVERVIEW:
Pelvic inflammatory disease (PID) is infection affecting upper genital tract in women, it usually ascends from the endocervix and if untreated will eventually lead to endometritis, salpingitis, parametritis, oophoritis, tubo-ovarian abscess and/or pelvic peritonitis. Neglected infections can become severe with long term sequelae.

INCIDENCE:
1% in reproductive age group
2% in 20-24 years age
5% of all gynaecological admissions
30% responsible for infertility
50% of patients with ectopic pregnancy, chronic pain, adhesions
Uncomplicated PID can be simple (compatible with outpatient management) or intermediate (requiring hospitalization for diagnostic uncertainty, symptom intensity, difficulties with oral antibiotics, previous treatment failure, or psychosocial distress).

ETIOLOGY AND RISK FACTORS:
Various pathogens have been implicated in causing PID and vary worldwide. STI in 60-75%, Pyogenic in 15-20%, Tubercular in 5% cases. Among the common pathogens, Chlamydia trachomatis and Neisseria gonorrhoeae are major. C trachomatis accounts for about 14-35% of cases.

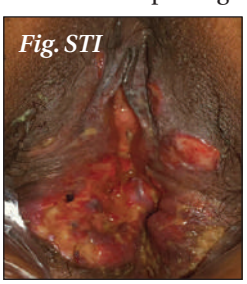
Fig. STI

Other pathogens like Mycoplasma genitalium, Gardnerella vaginalis, anaerobes (including Prevotella, Atopobium and Leptotrichia) are also inculpated. Microorganisms from the vaginal flora including streptococci, staphylococci, Escherichia coli and Haemophilus influenzae can be associated with upper genital tract inflammation. Others includes actinomycosis and schistosomiasis. Pathogen negative PID as well as PID with mixed infections is also common. A number of risk factors are associated with PID like young age, multiple partners, recent new partner (within previous three months), past history of sexually transmitted infections (STIs) in the patient or their partner, instrumentation of the uterus / interruption of the cervical barrier, termination of pregnancy, insertion of intrauterine device within the past six weeks etc. Some other risk factors include low socioeconomic status, cigarette smoking and douching.

CLINICAL FEATURES:
PID is a spectrum of symptomatology, depending on the severity, stage and the type of infection, it may be asymptomatic, minimally symptomatic or exhibit toxic symptoms of fever, nausea, vomiting, and severe pelvic and abdominal pain.
Gonococcal PID is thought to have an abrupt onset with more toxic symptoms than non-gonococcal disease. Gonorrhea and Chlamydia associated infections are more likely to cause symptoms toward the end of menses and in the first 10 days following menstruation.
The following symptoms are suggestive of a diagnosis of PID:
• Lower abdominal pain – usually bilateral, dull aching or crampy, and constant; it begins a few days after the onset of the last menstrual period and tends to be accentuated by motion, exercise, or coitus. Pain from PID usually lasts less than 7 days; if the pain lasts longer than 3 weeks, the likelihood that PID is the correct diagnosis declines substantially.
• Temperature higher than 38°C (found in 30% of cases), nausea, and vomiting manifest late in the clinical course of the disease.
• Deep dyspareunia – especially recent in onset.
• Abnormal bleeding – intermenstrual bleeding, postcoital bleeding and menorrhagia can occur secondary to associated cervicitis and endometritis.
• Unanticipated vaginal bleeding, often postcoital, is reported in about 40% of cases.
• Abnormal vaginal or cervical discharge – as a result of associated cervicitis, endometritis or bacterial vaginosis is present in approximately 75% of cases.

SIGNS:
• Rebound lower abdominal tenderness and involuntary guarding may be noted and suggest associated peritonitis.
• Right upper quadrant tenderness, especially if associated with jaundice, may indicate associated Fitz-Hugh–Curtis syndrome.
• Adnexal fullness or disproportionate unilateral adnexal tenderness may indicate the development of a tubo-ovarian abscess (TOA).
• Mucopurulent cervicitis is common and, if ab-

sent, has substantial negative predictive value.

DIAGNOSIS:

No single test is highly specific and sensitive for PID; however, a number of tests may be used to increase the specificity of the clinical diagnosis.

Table 1: PID diagnostic criteria as per 2015 CDC guidelines

Notes: Reproduced from CDC (US Centers for Disease Control and Prevention). 2015 Sexually Transmitted Diseases Treatment Guidelines. a - Initiate treatment if one or more of these criteria are met. b - In addition to one or more minimal criteria, one or more of the additional criteria increases specificity of the diagnosis of PID. c - One or more of these criteria provides the most specific diagnosis of PID.

Minimal clinical criteria-a	• Cervical motion tenderness • Uterine tenderness • Adnexal tenderness
Additional criteria- b	• Oral temperature greater than 101°F (38.3°C) • Abnormal cervical mucopurulent discharge or cervical friability • Abundant white blood cells on microscopic evaluation of vaginal fluid • Elevated erythrocyte sedimentation rate • Elevated C-reactive protein • Laboratory documentation of cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*
Specific criteria-c	• Endometrial biopsy with histopathologic evidence of endometritis • Transvaginal ultrasound or magnetic resonance imaging showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies suggesting pelvic infection • Laparoscopic findings consistent with PID

Laparoscopy is significantly more specific and sensitive than clinical criteria alone in the diagnosis of PID. The minimum criteria include tubal wall edema, visible hyperemia of the tubal surface, and the presence of exudate on the tubal surfaces and fimbriae. Pelvic masses consistent with TOA or ectopic pregnancy can be directly visualized. Hepatic abscess exudate or adhesions may be visible. Material can be obtained for definitive culture and histologic studies.

OTHER MODALITIES:

1. Ultrasound Imaging
2. Computed Tomography (CT)
3. MRI
4. Culdocentesis

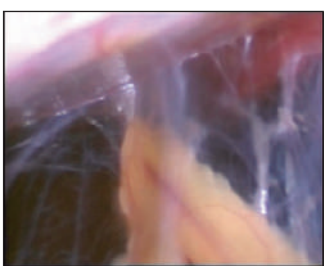

Fig. Fitz Hugh Curtis syndrome

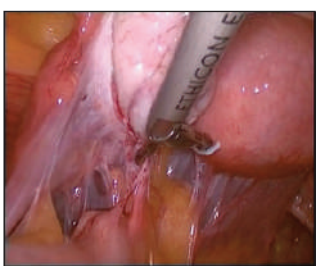

Fig. Chronic PID with adhesions

5. Endometrial Biopsy

CLASSIFICATION:

The Gainesville clinical classification of the disease divided into 5 stages:

1. Stage I - Salpingitis without peritonitis. This can be treated on outpatient basis.
2. Stage II - Salpingitis with peritonitis requiring hospitalization and intravenous antibiotic therapy.
3. Stage III - PID with pelvic mass.
4. Stage IV - Ruptured tubo-ovarian abscess.
5. Stage V - Tubercular salpingitis.

TREATMENT:

Treatment of PID aims at the relief of acute symptoms, eradication of current infection, and minimization of the risk of long-term sequelae. These sequelae, including chronic pelvic pain, ectopic pregnancy, tubal factor infertility (TFI), and implantation failure with in vitro fertilization attempts, may occur in as many as 25% of patients. Broad spectrum antibiotic therapy is required to cover N gonorrhoeae, C trachomatis and anaerobic infections. It is also desirable to include microbiological cover for other possible pathogens (e.g. M genitalium, streptococci, staphylococci, E coli, H influenzae).

Parenteral and oral antibiotic regimens have been found to have similar efficacy in women with mild to moderately severe PID, and Smith et al demonstrated that inpatient hospitalization for the treatment of PID is not economically feasible; therefore, the CDC recommends oral regimens in this subgroup of patients in the outpatient setting.

Inpatient treatment is recommended for patients who meet any of the following criteria: 1) unable to exclude a surgical emergency, 2) tubo-ovarian abscess, 3) pregnancy, 4) severe illness (eg, nausea, vomiting, and high fever), 5) inability to tolerate outpatient regimen, and 6) failure to respond to oral regimen with persistent and/or worsening symptoms. All patients should be re-evaluated by a clinician within 72 hours after initiating treatment. Additional evaluation and/or hospitalization for parenteral antibiotics may be indicated for patients who do not show clinical improvement at this time.

INFERTILITY & PID

• Impaired fertility is a major concern in women with a history of PID. Infection and inflammation can lead to scarring and adhesions within tubal lumens.

• TFI ranks among the most common causes of infertility, accounting for 30% of female infertility. Of women with TFI, 50% have no history of PID but have scarring of the fallopian tubes and exhibit antibodies to C trachomatis. Approximately 15% of women with PID develop TFI.

• The rate of infertility increases with the number of episodes of infection.

• The risk of ectopic pregnancy is increased 15-50% in women with a history of PID.

TREATMENT OF TFI

• Many variables need to be taken into consideration when counselling patients with tubal infertility regarding corrective surgery or IVF. The age of the patient, ovarian reserve, prior fertility, number of children desired, site and extent of the tubal disease, presence of other infertility factors, experience of the surgeon, and success rates of the IVF program are the most important.

• The advantages and disadvantages of IVF and tubal surgery need to be reviewed with the patient to provide assistance in her decision making.

• Overall, tubal surgery is a very poor alternative to IVF. Infertility associated with tubal blockage, especially if due to PID, is an absolute indication for IVF. In fact, any tubal damage due to PID, whether or not it is associated with blockage is an indication for IVF.

PROCEDURES FOR PROXIMAL TUBAL BLOCKAGE

Proximal tubal blockage accounts for 10%–25% of tubal disease.

Unless the proximal blockage on HSG is clearly due to SIN, selective salpingography or tubal cannulation can be attempted. If the obstruction is not overcome by tubal cannulation with gentle pressure, in such cases, IVF is preferred to resection and microsurgical anastomosis. IVF would also be the preferred treatment for proximal tubal blockage in older women and in the presence of significant male factor infertility.

SURGERY FOR DISTAL TUBAL DISEASE

GOOD PROGNOSIS

Distal tubal disease includes hydrosalpinges and fimbrial phimosis. A good prognosis is associated with patients who have mildly dilated tubes (<3 cm) with thin and pliable walls, and a lush endosalpinx with preservation of the mucosal folds.

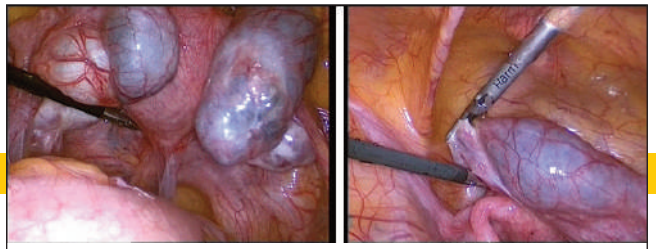

Fig. B/L Hydrosalpinges *Fig. Hydrosalpinx*

Laparoscopic neosalpingostomy and fimbrioplasty are carried out by opening a hydrosalpinx or increasing the opening or fimbrial phimosis, respectively. The fimbria are then everted and secured to the tubal serosa with sutures or electrosurgery (Bruhat procedure). IVF is preferred over salpingostomy for mild hydrosalpinges in older women and for those with male factor or other infertility factors.

POOR PROGNOSIS

Patients having a poor prognosis may have extensive dense peritubal adhesions, massively dilated tubes with thick fibrotic walls, and/or sparse or absent luminal mucosa. Laparoscopic salpingectomy is indicated when the fallopian tube is damaged beyond repair by infection, endometriosis, or ectopic pregnancy. Cochrane analysis concluded that laparoscopic salpingectomy or occlusion should be considered before IVF for women with communicating hydrosalpinges. Even patients with a unilateral hydrosalpinx have been shown to have lower pregnancy rates with IVF.

There are no adequate trials comparing pregnancy rates with tubal surgery vs. IVF. However, IVF has a higher per-cycle pregnancy rate. Laparoscopic salpingectomy or proximal tubal ligation overcomes the detrimental effect of hydrosalpinges on IVF pregnancy rates in patients who are not candidates for corrective tubal surgery.

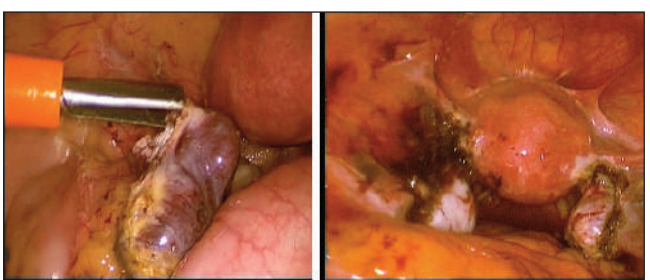

Fig. Salpingectomy *Fig. B/L Salpingectomy*

TAKE HOME MESSAGE:

1. PID involves upper genital tract viz tubes, endometrium and cervix by variety of pyogenic and non pyogenic microbes invading the defences at various levels.
2. Laparoscopic diagnosis is the gold standard along with clinical, microbiological and histopathological examination that helps in clinching diagnosis.
3. Appropriate and adequate oral or parenteral antibiotics to the patient and partner is key to success to prevent complications and sequelae.
4. Laparoscopic tubal clipping, linear salpingostomy and definitive treatment by salpingectomy improves success in IVF.

LAPAROSCOPIC OVARIAN DRILLING

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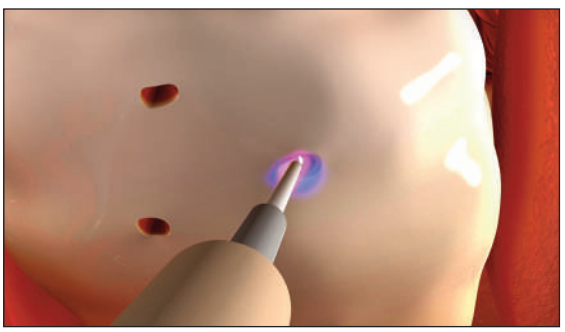

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common condition affecting 8% to 13% of reproductive aged women. Diagnosis is made using the Rotterdam criteria in which a minimum of 2 out of 3 findings viz irregular cycles, ultrasound findings of polycystic ovaries, clinical or biochemical hyperandrogenism should be present to diagnose the condition.

In the past clomiphene citrate (CC) used to be the first-line treatment in women with PCOS. Clomiphene resistance is defined as failure to ovulate with a maximum dose of clomiphene citrate (150mg daily for 5 days) for atleast 3 cycles. Approximately 20% of women on CC are CC-resistant and can be treated with gonadotrophins or other medical ovulation-induction agents. Ovulation induction with letrozole should be the first-line treatment according to new guidelines, but the use of letrozole is off-label. Consequently, CC is still commonly used.

Clomiphene and letrozole are not always successful, can be time consuming and can cause adverse events like multiple pregnancies and cycle cancellation due to an excessive response.

Stein and Cohen in 1935 first reported successful treatment of polycystic ovarian syndrome by performing a wedge resection of the ovary. This technique has now been abandoned and the modern surgical alternative to wedge resection is laparoscopic ovarian drilling (LOD).

INDICATION

In todays era the only indication for laparoscopic ovarian drilling is clomiphene resistance.

Some authors have reported additional benefits like reduction in androgenic symptoms but performing a drilling just for reduction in these features in the absence of clomiphene resistance is not justified.

MECHANISM OF ACTION

Ovarian drilling acts in a similar way to wedge resection. There is destruction of the ovarian cortex and stroma and drainage of small, androgenic follicles. This leads to a fall in intraovarian androgen levels and androgen production. Consecutively, the peripheral conversion of androgens to oestrogens is reduced, resulting in reduction of LH hypersecretion from the pituitary. This leads to a conversion of the androgenic environment into an estrogenic environment and restoration of normal follicular recruitment.

INSTRUMENTS NEEDED

For laparoscopic ovarian drilling, one will need a laparoscope, camera, light source, insufflator, ports for inserting instruments, graspers, suction and irrigation cannula and a ovarian drilling needle. The needle should be insulated upto the tip to minimise current related complications.

TECHNIQUE

The laparoscopic approach to ovarian drilling as a substitute of open surgical wedge resection was firstly described by Gjönnaess in 1984. A monopolar electrosurgical needle electrode is used to penetrate the ovarian capsule at a number of points with the aid of a short burst of diathermy. The ovary should be stabilised by grasping the ovarian ligament and the needle should enter perpendicular to the ovarian surface. A monopolar coagulating current is used. Rule of 4 is commonly followed which states 4 punctures for 4 seconds each at 40W on each ovary which delivers a total dose of around 640J of energy per ovary. Each ovary is then cooled by irrigation using physiological solution ie ringer's lactate.

Another method to adjust the dose of energy is to perform an ultrasound assessement of the ovarian volume and then subsequently adjust the dose to deliver 60J/cm3. The current can then be delivered by dividing the total dose using the following example. If the ovarian volume is 10cm3, the total dose would be 600J/ovary. This can be then divided into 5 holes of 3 seconds duration at 40W setting leading to a total dose of 600J/ovary. Reducing the thermal energy (<300 J/ovary) and/or number of punctures (2/ovary) reduces the chances of spontaneous ovulation and conception, while higher thermal doses (>1000

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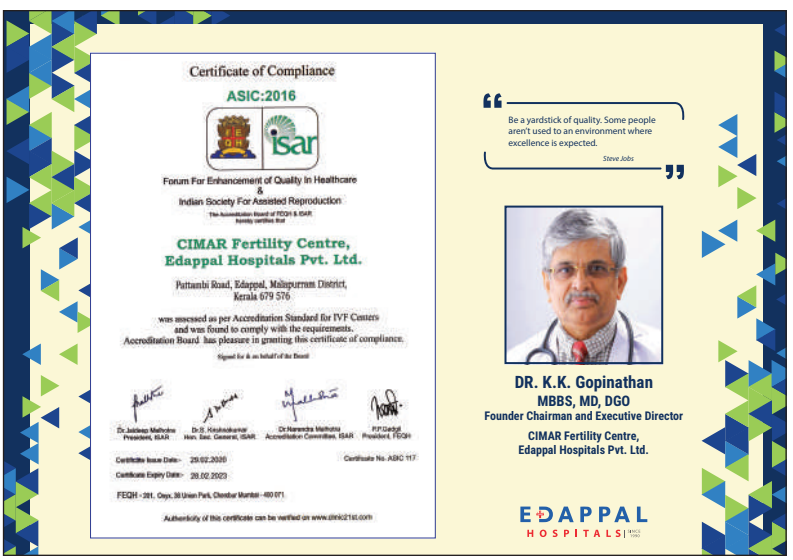
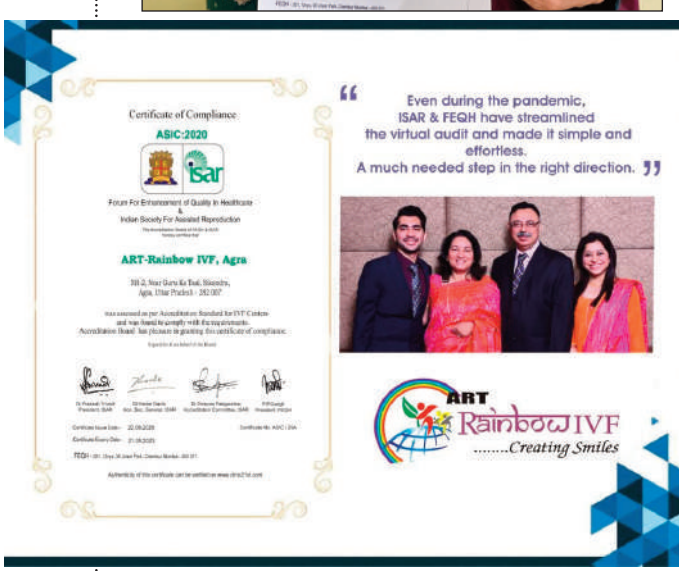
Dr Asha Rao, Coimbatore





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"Thanks to this accreditation, we learnt about maintaining a logbook of all equipment, and maintaining liquid nitrogen protective gear. The committee members were helpful at every step." - **Dr Prasenjit Kumar Roy and Dr Shefali Bansal Madhav**

J/ovary) and/or number of punctures (≥7/ovary) causes extensive tissue destruction without additional improvement in outcomes.

RISKS/COMPLICATIONS

Besides the risks of general anesthesia and surgery, the biggest concern with ovarian drilling is considered to be formation of de-novo adhesions. Adhesion rates ranging between 0 to 70% have been reported. However there is no need for a second look laparoscopy for adhesiolysis since patients with adhesions also have similarly high pregnancy rates.

Another cause for worry is destruction of too much of ovarian tissue leading to a reduction in ovarian reserve. Therefore it is imperative to avoid over-zealous use of energy during the surgery.

Sometimes there might be bleeding from the drilling site. Options to achieve hemostasis include applying pressure over the puncture site for 2 to 3 minutes (corresponding to the patients bleeding time). Grasping the infundibulopelvic ligament and the ovarian pedicle also may help in hemostasis. Use of hemostatic agents like feracrylium can be employed as an adjunctive . Sometimes small vessels running over the surface of the ovary get injured. This can be tackled with a short burst of bipolar energy. One should avoid using excessive monopolar coagulation current in the same hole for hemostasis as it may lead to undue destruction of the ovarian tissue and depletion of ovarian reserve.

RESULTS

Reports on ovarian drilling reveal excellent results. Even clomiphene-resistant patients show a high rate of spontaneous ovulations after the laparoscopic procedure. The original work by Gjönnaess describes an ovulation rate of 92% and a pregnancy rate of 80%. Six months after drilling, standard ovulation rates are between 63% and 81% [31, 32, 43]. The effect usually lasts upto a year but may be longer too in some cases. The pregnancy rate is around 50% and most pregnancies happen within a year.

Prognostic Factors Affecting the Success of the Procedure

Prognostic factors adversely affecting the results of ovarian drilling include:

- High BMI
- Age >30years
- Low SHBG
- Low LH levels (<10IU/L)
- Duration of infertility >3 years
- Insulin resistance
- Associated male or tubal factor

UNILATERAL VS BILATERAL OVARIAN DRILLING

Unilateral ovarian drilling when compared to bilateral ovarian drilling has similar effects in terms of resumption of ovulation and pregnancy rates within a 3 month period. The drop in AMH is also significantly lesser. However the effect is short lived with significantly lower ovulation and pregnancy rates at 6 months. It may be used in cases with uneven ovarian size and in patients where the AMH is not grossly elevated.

REPEAT OVARIAN DRILLING

A study reported the effectiveness of repeat ovarian drilling in women who had previously shown response to ovarian drilling. However the study was a retrospective analysis with only 20 patients. Another retrospective study reported repeat ovarian drilling for 33 women using a transvaginal hydrolaparoscopic approach. The patients who underwent second drilling had similar preoperative AMH levels to when the first procedure was performed. They reported a pregnancy rate of 57.6% with 52.6% spontaneous pregnancies. Women who responded only with a second drilling when compared to those patients who responded with a single drilling had significantly higher preoperative AFC (61 vs 48.8) and AMH (16.5 vs 12.9). With a variety of non-invasive alternatives available repeat ovarian drilling should be discouraged.

IMPACT ON OVARIAN RESERVE

There have been concerns laparoscopic ovarian drilling and destruction of ovarian tissue on the ovarian reserve. A recent meta-analysis reported a significant fall in the AMH levels following ovarian drilling. However the authors were uncertain regarding whether the fall of AMH was a normalization of the elevated pre-operative AMH levels rather than true destruction of the ovarian reserve. There may be upto 30% fall in AMH levels in around 25% patients. It is still imperative to follow the dose calculation and not be overzealous while performing ovarian drilling to prevent detrimental effects on the ovarian reserve.

ALTERNATIVE APPROACHES TO MONOPOLAR OVARIAN DRILLING

An alternative approach to ovarian drilling is the transvaginal hydrolaparoscopic approach. It was first described by Gordts et al in 1998. In this approach, a veress needle is inserted in the posterior fornix and the pelvis is flooded with around 300-400ml saline. A specially designed trocar is inserted through the posterior fornix following which the telescope is inserted. The ovaries are visualized and punctured using a 5 Fr bipolar needle electrode. Around 10-15 punctures are made at a current setting of 130W. Cumulative pregnancy rates (spontaneous and stimulated non ART cycles) have been reported to be around 60% within a year when done for patients with clomiphene resistance. However the procedure needs additional training, shouldn't be done when pelvic adhesions or deformities are suspected, and there are no studies comparing the technique with traditional laparoscopic ovarian drilling. Traditional Laparoscopic ovarian drilling using a bipolar electrode has been reported with upto around 80% successful resumption of ovulation but

no data on pregnancy rates. Other methods have also been reported like use of a monopolar hook electrode, harmonic scalpel, CO2, Argon and ND YAG lasers. However, larger prospective studies are needed to validate the use, safety, efficacy and long-term effects of these alternate techniques.

ULTRASOUND GUIDED TRANSVAGINAL OVARIAN PUNCTURE

Ultrasound guided transvaginal ovarian puncture can be performed, under general anesthesia with Propofol, using a 16-gauge, 35-cm long sharp needle connected to a continuous manual vacuum pressure. Each ovary has to be repeatedly punctured from different angles with between three and six punctures, and all the small follicles visible by ultrasound are to be aspirated. Patients can be discharged after 2–3 hours after transvaginal ultrasound to rule out any complications of the procedure.

When compared with laparoscopic ovarian drilling, results of transvaginal needle puncture are not significantly different with regard to resumption of normal menstruation, hirsutism, acne, ovulation, and pregnancy. Correction of AMH levels is lesser compared with ovarian drilling. The procedure is relatively quicker and less invasive and can avoid current related problems. As per a metaanalysis by Cochrane, the ovulation rate is slightly lower when compare with laparoscopic ovarian drilling. This conclusion was based on low quality evidence and in the absence of well designed large randomized controlled trials it is difficult to recommend this method over traditional ovarian drilling.

OVARIAN DRILLING VS GONADOTROPINS

Gonadotropins are effective agents for ovulation induction in patients with clomiphene citrate resistance. When compared to ovarian drilling, it is a less invasive procedure but needs intense ultrasound monitoring in each cycle. In a recent metaanalysis comparing ovarian drilling with gonadotropins, there is a slightly lower pregnancy rate (OR 0.71, 95% CI 0.54 to 0.920) but no differences in clinical pregnancy rate (OR 0.86, 95% CI 0.72 to 1.03). There is a significantly lower rate of multiple pregnancy (OR 0.34, 95% CI 0.18 to 0.66) and OHSS (OR 0.25, 95% CI 0.07 to 0.91). There is no significant difference in the miscarriage rates.

In a cost analysis ovarian drilling and gonadotropin ovulation induction were compared. It was found that both groups had similar pregnancy rates and live birth rates but the cost of treatment, cost per pregnancy and the cost per live birth was significantly lesser in the ovarian drilling group. However the costs per pregnancy were found to be higher in patients undergoing ovarian drilling if they require subsequent ovarian stimulation with oral ovulogens or gonadotropins.

OVARIAN DRILLING VS LETROZOLE

Letrozole, an aromatase inhibitor, has good potential for inducing ovulation in women with PCOS without exerting antiestrogenic effects on the endometrium. It promotes mono-follicular development and is effective in women with clomiphene resistance. A recent meta-analysis comparing letrozole vs ovarian drilling reported a significant increase in clinical pregnancy rates and endometrial thickness on the day of HCG with letrozole but no significant difference in ovulation rates, live birth rates and abortion rates. Letrozole may be an effective alternative to laparoscopic ovarian drilling. There is insufficient data on the effect of ovarian drilling in patients resistant to letrozole.

Recommendations from the International Evidence Based Guideline for Assessment and Management of Polycystic Ovary Syndrome 2018.

• Laparoscopic ovarian surgery could be second line therapy for women with PCOS,
who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors.
• Laparoscopic ovarian surgery could potentially be offered as first line treatment if
• Laparoscopy is indicated for another reason in women with PCOS with anovulatory
infertility and no other infertility factors
• Risks need to be explained to all women with PCOS considering laparoscopic ovarian surgery
• Where laparoscopic ovarian surgery is to be recommended, the following need to be considered:
• Comparative cost
• Expertise required for use in ovulation induction
• Intra-operative and post-operative risks are higher in women who are overweight and obese
• There may be a small associated risk of lower ovarian reserve or loss of ovarian function
• Periadnexal adhesion formation may be an associated risk

CONCLUSION

Laparoscopic ovarian drilling is an effective tool in the gynecologists arsenal to treat PCOS. It is a single step procedure with high ovulation and pregnancy rates, leads to mono-follicular development and singleton pregnancy, longer duration of action. It doesn't need frequent ultrasounds for ovulation monitoring and in some settings is cost effective and logistically friendly. However it is an invasive procedure and the risks of hampering the ovarian reserve and adhesion formation should be considered. Patient characteristics should be evaluated before offering this procedure. The use of energy should be judicious to avoid detrimental effect on the ovarian reserve. Newer approaches and energy sources may reduce the invasiveness and the complications of the procedure.

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Jharkhand State Chapter Contribution

FERTILITY PRESERVATION IN THE CONTEXT OF PELVIC RADIOTHERAPY

INTRODUCTION

Increasingly, women are presenting in fertility services with history of childhood cancer or if advanced age, of cancers of early adulthood having received pelvic radiotherapy as treatment. Many cancer survivors are unaware of the potential long term consequences of their treatment which includes fertility issues or even which treatment they have had. It thus becomes imperative that women and young girls are made aware of various options for fertility preservation they may choose from before embarking on the journey of cancer treatment. Cancer treatment options include surgery, radiotherapy, chemotherapy, targeted biological therapy and hormonal therapy. All these therapies are used individually or in combination depending upon the cancer type. However all these treatment regimens cause destruction of some healthy tissue as a necessary by-product and thus emphasis is to develop more precise targeted agents which spare the healthy tissue. The long term consequences of cancer therapy can occur soon after treatment or many years later and they pertain to specific cancer treatments rather than cancer itself. The North American Childhood Cancers Survivors Study (CCSS) has shown that among the survivors of childhood cancer 62.5% had at least one chronic medical condition. The risk is much higher in patients receiving treatments in the form of radiotherapy and chemotherapy.

Cancer survivors who underwent radiotherapy to the pelvis, preservation ovarian function and endometrial and myometrial functionality remains a major clinical challenge. Overcoming these would offer the patients a chance for both cancer control and fertility preservation.

EFFECTS OF PELVIC RADIOTHERAPY ON FERTILITY

1. Effect on ovarian function: The ovaries are sensitive to irradiation with the resulting dam-

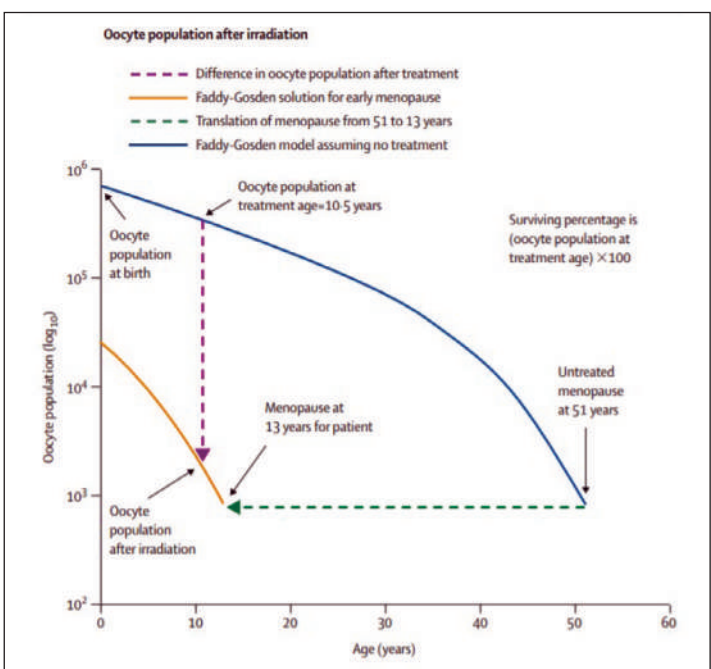

Figure 1: Faddy-Gosden model[7]: This model determines the size of the oocyte pool for any age from birth to menopause (estimated at 51 years). Graph shows the calculation of an estimated surviving fraction for a patient treated at age 10.5 years with whole-body irradiation (14.4 Gy) who developed ovarian failure at age 13 years, which was 0.56%.

Table 1: Potential long term complications of radiotherapy

Site of radiotherapy	Type of cancer	Potential long term consequences
Cranial	Brain malignancies	Hypopituitary effects
Neck	Thyroid cancer, hodgkin's lymphoma	Thyroid dysfunction
Mediastinum/Chest	Hodgkin's lymphoma, breast cancer	Cardiac and respiratory effects
Abdominal	Neuroblastoma, Wilm's tumour	Diabetes
Total body	Pre-bone marrow transplantation for leukaemia	All above effects but at lower rates

age depending upon the treatment field, total dose, number of fractions and age at the time of treatment. Fractionation reduces the time available for repair and thus can be detrimental for the ovaries.In female patients, whole-body, abdominal, or pelvic irradiation will cause ovarian damage and could also affect uterine function. Depletion of the number of primordial oocytes after radiotherapy is proportional to the size of the oocyte pool, as shown by the FaddyGosden model. Therefore, the younger patients are at the time of radiotherapy,develop late onset of premature menopause for a given dose of radiation.
Effective sterilising doses are 20.3 Gy at birth, 18.4 Gy at 10 years, 16.5 Gy at 20 years, and 14.3 Gy at 30 years.

2. Effect on uterine function: Radiotherapy affecting the uterus in childhood and adolescence increases the incidence of spontaneous miscarriage, intrauterine growth restriction and premature deliveries. Probable mechanisms have been described as secondary to reduced elasticity of the uterine musculature and uterine vascular damage.

FERTILITY PRESERVATION TECHNIQUES
1. Ovarian function preservation: Patients planned for pelvic radiation can have their ovaries removed from the radiation field, a procedure known as ovarian transposition which can be done laparoscopically. Although ovarian function can be preserved with such techniques, radiation induced uterine damage will reduce the chances of a successful pregnancy. This procedure can cause ovarian function preservation in 70-100% patients. The complications include ovarian metastasis,pain, injury to ovarian vessels, torsion, inflammation and failure to preserve ovarian function. Another established option is oocyte stimulation and cryopreservation of embryos following IVF technique or cryopreservation of oocytes in patients without a partner. Alternatively,ovarian tissue might be removed and cryopreserved to be re-implanted later preferably by an orthotopic approach, a procedure not requiring a partner or hormonal stimulation.However, following radiotherapy the vascular supply will be impaired and heterotopic transplantation to a remote site may be required. In 2004, first live birth was reported after cryopreservation of ovarian tissue followed by transplant in a women with Hodgkin's lymphoma. To the best of our knowledge the birth of at least 18 healthy babies has been reported after trans plantation of frozen-thawed human ovarian tissue.
2. Uterine function preservation: Uterine transplantation is an emerging viable fertility option for patients

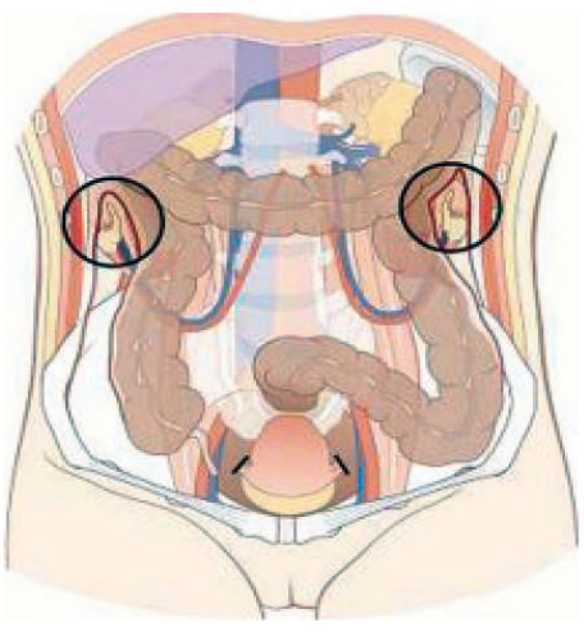

Figure 2: Hwang et al. demonstrated that fixation more than 1.5 cm above iliac crest was the most important factor for intact ovarian function[8]. The figure shows mobilisation of both the ovaries along the ovarian vessels and fixing them in the paracolic gutters as high and lateral as possible.

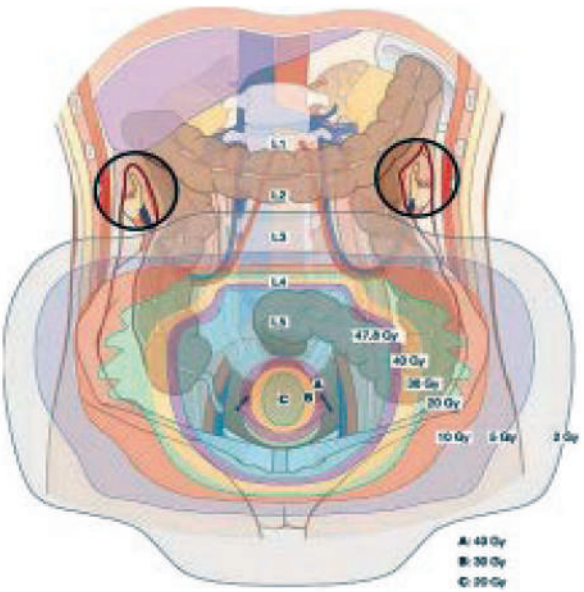

Figure 3: Isodoses of the prescribed dose (47.8 Gy) in the target volume decreasing to the periphery and to the ovaries (in black circles) to < 2 Gy between second (L2) and third (L3) lumbar vertebra.

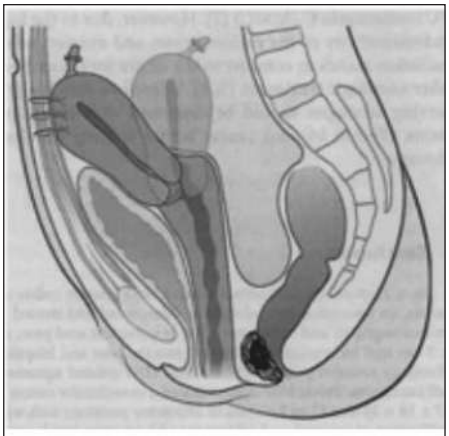

Figure 4: Another potential uterine preservation option in cases of colon and rectal cancer radiotherapy is uterine ventral fixation in which the uterine fundus is hitched to the anterior abdominal wall.

having undergone pelvic radiotherapy. The first uterine transplant from a multi-organ donor was undertaken in Turkey in 2011 and successfully achieved menstrual cycles after 20 days. There are currently reported 10 live births after uterine transplantation with 1 of then following cervical cancer. It has all the disadvantages of transplants in general, such as rejection, immunosuppressive therapy, and surgical complications in the living donors, as well as the need for a second surgical procedure to remove the uterus once the patient's family is complete. In patients requiring radiation to posterior pelvis such as rectal carcinoma, uterus can be fixed to the anterior abdominal wall to minimise the radiation dose received.

Uterine sparing pelvic radiation therapy has also been proposed as a novel treatment modality however much research needs to be done regarding its efficacy both in terms of optimal cancer treatment and fertility preservation.

However none of the above methods guarentee optimal uterine function and the techniques to allow pregnancy might make surrogacy necessary.Uterine and adnexal transposition (UT) to the upper abdomen before radiotherapy might protect these organs, and subsequent repositioning of the uterus into the pelvis might allow the patients to experience a normal pregnancy. In this technique, steps are similar to laparoscopic hysterectomy with the exception of preservation of both the infundibulopelvic ligaments which provide vascularity to the transposed uterus.

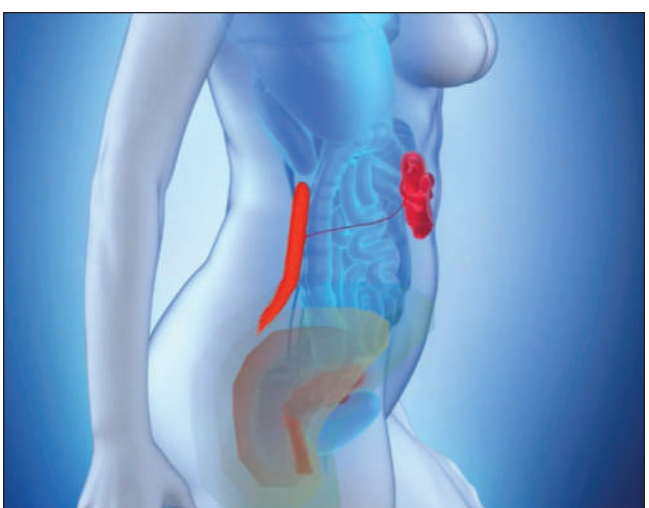

Figure 5: Uterine transposition technique in which the uterus along with bilateral adnexa is removed from the pelvic radiation field.

CHILDREN OF CANCER SURVIVORS

Although the above options offer real hope for fertility preservation, consideration should be given for the effect cancer treatment might have on their future children.There have been concerns regarding the possible mutational effect on gametes following radiotherapy which could predispose the children to congenital abnormalities or even cancer itself.However a large epidemiological study failed to show such link.

Neverthless, long-term surveillance of pregnancy outcome and child health remains essential after the use of assisted-conception technologies in survivors of cancer.

CONCLUSION

With the emerging advances in cancer treatment, many children and adolescents can realistically hope for long term survival. However they often have to bear the brunt of consequences of treatment, infertility being one of them. Thus methods of protecting or restoring infertility needs to be considered early on. However prediction of future fertility after treatment might be difficult, several potential therapeutic interventions are under research instilling genuine hope in young childhood cancer survivors.

ISAR ACCREDITED CLINIC

Overall it was a good experience and probably will be the same for any centre following ICMR norms. We would like to thank Team ISAR for the initiative.

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West Bengal State Chapter Contribution

THIN ENDOMETRIUM AND ART

INTRODUCTION

Successful embryo implantation requires an optimum embryonic development along with a receptive endometrium. Endometrial thickness (ET) is widely used as the prognostic factor for outcome and when assessed to be thin, physicians often opt for embryo freezing and not to proceed with fresh transfer. This guideline seeks to provide an evidence-based approach to the assessment and treatment of thin endometrium in ART cycles.

MEASUREMENT OF ENDOMETRIAL THICKNESS (ET)

Endometrial thickness (ET) is measured by transvaginal ultrasonography (USG) as the maximal distance between the echogenic interfaces of the myometrium and endometrium. In 10% of cases the ideal image for measurement is difficult to obtain due to the presence of fibroids, adenomyosis, polyps, uterine orientation, body habitus, previous surgeries and patient intolerance. Studies have shown that for endometrial measurements there are inter-observer variability of 1 mm and intra-observer variability of approximately 0.6 - 0.7 mm.

DEFINITION AND INCIDENCE OF THIN ENDOMETRIUM

The definition and cut off for thin endometrium differs, but most studies have used < 7 mm or < 8 mm of endometrial thickness (ET) on the day of human chorionic gonadotropin (hCG) administration. However pregnancies have been reported in ART cycles with ET as low as 3.8 mm on the day of hCG, although the chance of pregnancy is much lower in those with ET of < 4 mm. One study reported no live births from 11 embryo transfers in patients with ET between 4 and 4.9 mm and 4 live births from 29 embryo transfers in patients with ET between 5 and 5.9 mm. As yet there is no consensus on what defines a persistent thin endometrium in ART cycle and incidence of this phenomenon with regards to the number of affected cycles.
In fresh embryo transfer cycles, the incidence of ET < 7 mm on the day of hCG administration varies between 1% and 2.5%. A study using the Canadian ART database, which included 21,900 fresh embryo transfer cycles from 2012 to 2015, showed that ET was < 8 mm in 12.3% and < 7 mm in 3.9% of cases. Similarly, in 18,900 frozen thaw embryo transfer cycles, the ET was < 8 mm in 14.1% and < 7 mm in 3.1% of cases. This is likely to be an underestimate of the true incidence of thin endometrium in ART cycles, as this only represents cycles which proceeded to embryo transfer.

CAUSES OF THIN ENDOMETRIUM

Commonly described causes of thin endometrium include clomiphene citrate therapy, Asherman syndrome due to previous intrauterine surgery including endometrial curettage, genital tuberculosis, septic abortion, postpartum endometritis and pelvic irradiation. Studies on patients with thin endometrium have also reported Mullerian anomalies, submucous and intramural fibroids, adenomyosis, hypothalamic or hypogonadotrophic hypogonadism, primary ovarian failure like Turner's syndrome and premature ovarian insufficiency.

MANAGEMENT OF THIN ENDOMETRIUM IN FRESH EMBRYO TRANSFER

Oestradiol (E2) supplementation in the luteal phase starting from the day of hCG trigger or from the day of oocyte collection had been tried in women with thin endometrium. In a randomized controlled trial (RCT), high dose E2 luteal supplementation was found to be beneficial in improving implantation and pregnancy rates in women undergoing fresh embryo transfer with long GnRh agonist protocol. In a retrospective study on fresh embryo transfer, luteal phase E2 supplementation was also useful, only when the serum E2 level on the day of hCG trigger was < 1360 pg/ml. However, another retrospective cohort study on women with ET < 8 mm did not find any beneficial role with the addition of E2 supplementation. Finally, the Cochrane review also did not find any beneficial role of luteal E2 in addition to progesterone supplementation in improving pregnancy rate.
Changing the type and dosage of gonadotrophins in ovarian stimulation protocol

does not significantly reduce the incidence of thin endometrium and therefore, such practice is not recommended. One RCT found that women with thin endometrium on the day of hCG trigger can have better outcome if GnRH agonist injection is administered on the day of oocyte retrieval. Following fresh embryo transfer another GnRH injection is given in the mid luteal phase. However, further studies are needed to confirm the benefits.
Based on Canadian data of 22,000 fresh cycles, the Canadian Fertility and Andrology Society recommended elective cryopreservation of all the embryos and cancelling fresh transfer, if endometrium thickness is < 8 mm on the day of hCG trigger. Subsequent frozen transfer in oestrogen replaced cycle has been found to significantly improve pregnancy rates.

MANAGEMENT OF THIN ENDOMETRIUM IN FROZEN EMBRYO TRANSFER (FET)

Different methods of endometrial preparation are used for FET cycles:
1) natural cycle, 2) modified natural cycle, 3) hormone replacement cycle with or without down-regulation with GnRh agonists and 4) ovarian stimulation cycles. In terms of thin endometrium, there are no high quality studies comparing between these protocols in improving endometrial thickness (ET). However, in practice, clinicians often switch between natural cycles and hormone replacement cycles if they find difficulty in achieving optimum ET of > 7 mm with one particular protocol.
In hormone replacement cycle, E2 therapy should be started as soon as possible, preferably before day 4 of the cycle for effective suppression of follicular development. Various forms of E2 are commonly used for this purpose, including different oral tablets of micronized E2 (valerate and hemihydrates) and transdermal E2 gels. Serum E2 levels (>200 pg/ml) and ET remain similar between these preparations and pregnancy rates are also not different. However, transdermal preparation is associated with more physiological oestrone : oestradiol (E1 : E2) level as it effectively bypasses hepatic metabolism. Vaginal E2 is not used as it is unable to achieve the same serum concentration and can damage the action of vaginal progesterone, if used together used for luteal phase support.
The question is how long E2 therapy can be used in case of suboptimum endometrial thickness. One study used it for 14-82 days (mean duration 30 days) in women who had thin endometrium during ovarian stimulation. They found better ET and pregnancy rates without any significant adverse reactions on prolonged use of E2 therapy. However, another cohort study on 1377 frozen blastocyst transfer cycles found significant reduction in live birth rates if duration of E2 therapy was more than 28 days before embryo transfer. In contrast a retrospective cohort study on 1439 cycles with euploid blastocyst transfer confirmed that duration of E2 therapy did not affect pregnancy, live birth and miscarriage rates. However, the same study found that each extra day of E2 therapy was associated with reduction in gestational age at delivery, although it did not increase the risk of preterm delivery significantly.

USE OF ADJUVANTS IN WOMEN WITH THIN ENDOMETRIUM

A number of "add-on" therapies have been tried in order to improve endometrial thickness (ET) in refractory cases but none of them have been really effective.
Low dose aspirin is commonly used "empirically" as add-on in ART, even though it is not supported by sufficient scientific evidence. Only one RCT looked into effectiveness of aspirin therapy in thin endometrium and did not find any beneficial role.
Since Sildenafil citrate improves endometrial blood flow, it has been used in women with thin endometrium. Similar to low dose aspirin, again only one RCT found significant thickening of endometrium with sildenafil citrate therapy, although that did not translate into better pregnancy rate.
Low dose hCG (150 IU/day) supplementation during proliferative phase of oestrogen replacement cycles in women with thin endometrium was found beneficial in two case series but this approach is yet to become popular in regular clinical practice.
Use of pentoxifylline, L-ariginine, vitamin C and vitamin E in women with thin endometrium are based on case series and small observational studies, none of which could show definite improvement and therefore, their use is not recommended.

ROLE OF GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF)

G-CSF is a glycoprotein produced by bone marrow cells, stromal cells, fibroblasts, macrophages and endothelial cells, and also by reproductive cells like ovary and endometrium. It stimulates neutrophilic granulocyte proliferation and differentiation. By promoting cytokine secretion and activating T-regulatory cells, it influences local immune modulation and vascular remodeling in endometrium. Its efficacy has been confirmed by many studies in both fresh and frozen embryo transfer cycles in women with resistant thin endometrium, although some studies have suggested no improvement on clinical outcome in spite of increase in ET. Subsequently, the use of this molecule has been expanded to women with recurrent implantation failure and recurrent pregnancy loss.
Intrauterine instillation of G-CSF appears to be the

most widely practiced route of administration, although there are smaller series of subcutaneous injection reported by others. A meta-analysis showed that G-CSF administered subcutaneously also resulted in higher implantation and clinical pregnancy rates compared to the control group with no G-CSF treatment. A single dose intrauterine infusion of 300 mcg has been used by most of the studies, with the exception of a few newer series reporting use of a second dose. Similarly, a single dose of 300 mcg or multiple doses of 60 mcg G-CSF, through subcutaneous route have also been reported. Contraindications for G-CSF treatment are rare but include sickle cell disease, chronic neutropenia, known past or present malignancy, renal insufficiency, upper respiratory infection, pneumonia, and congenital fructose intolerance. Mild and temporary side effects of G-CSF are general fatigue, headache, bone pain, insomnia and gastrointestinal disturbances. Anaphylactic shock, chest pain and syncope may occur on rare occasions. Intrauterine administration however has negligible side effects in comparison to the subcutaneous route.

ROLE OF PLATELET RICH PLASMA (PRP)

Autologous PRP is prepared from individual's fresh whole blood, which is centrifuged to remove red blood cells and the remaining plasma has a 5 to 10 folds of higher concentration of platelet that helps to increase the release of essentials growth factors like VEGF, EGF, PDGF and other cytokines. It has found its application in multiple specialties in order to promote natural healing responses. It has also been used for ART in cases of premature ovarian failure, recurrent implantation failure and refractory endometrium.

A higher concentration of various growth factors in PRP is the possible mechanism behind its potential to increase ET. About 10–20 ml of venous blood is needed which yields 1–2 ml of PRP. The commonest mode of administration is by intrauterine perfusion, but hysteroscopy-guided sub-mucosal injection of the endometrium as a novel technique has also been described. Several studies have shown significant increase in ET resulting in lower cycle cancellation rates, as well as improved outcome of ART treatment with higher implantation, clinical pregnancy and live birth rates. PRP being an autologous material, no definite side effects of its administration has been reported so far.

In a pilot study on 10 patients with a history of ART cycle cancellation due to inadequate endometrial growth (< 7 mm), ET increased 48 hours after the first PRP instillation and reached > 7 mm after the second PRP dose in all patients. However, a double blind RCT reported no significant increase in ET after the first dose but all patients had increase in ET following the second dose. In another pilot study, PRP was injected into subendometrial region under hysteroscopic guidance in the cycle prior to FET. They reported a significant growth in ET and an increase in pregnancy rate. A recent meta-analysis also reported endometrial expansion along with an increase in implantation and chemical pregnancy rates with the use of PRP in patients with persistently thin endometrium.

CONCLUSIONS

Thin endometrium is frustrating and at the same time a challenging scenario in ART treatment, affecting both fresh and frozen embryo transfer cycles. With the availability of vitrification, the option of embryo freezing and transfer of frozen-thawed embryos in a subsequent cycle remains an effective alternate solution. Currently there is lack of strong evidence to support any specific protocols of ovarian stimulation or adjuvant therapies to improve pregnancy outcome in women with thin endometrium, although G-CSF and PRP are only therapies that are showing promises of better outcome.

There is a wide range of evidence to suggest that G-CSF provides endometrial growth in cases of refractory thin endometrium, and subsequent higher implantation as well as clinical pregnancy rates. On the contrary, there are some reports to suggest that the treatment outcomes may not improve despite documented endometrial growth. Such a diversity of evidence is possibly due to the fact that different studies have reported the use of the drug for varied indications, at various stages of ART cycle and in different dosage using different route of administration. Most importantly, the molecule is well tolerated and without serious side effects in women undergoing ART.

Intrauterine PRP administration has shown promising results in enhancing endometrial thickness, which naturally translates to improved implantation and clinical pregnancy rates. No definite side effects of PRP administration has been reported so far, by virtue of its autologous nature. Therefore, it may be considered as an effective and safe mode of treatment for refractory thin endometrium in patients undergoing ART cycles.

No uniform consensus or guideline has evolved till date regarding the route of administration, dosage and timing of administration of G-CSF as well as PRP. Therefore, more evidence based studies, conducted on larger population to understand the efficacy of the newer drugs are essential to arrive at further robust conclusions. Moreover, different stem cell researches are underway towards an effective solution for women with persistently thin endometrium during ART cycles.

USAGE OF ESTROGEN IN ENDOMETRIAL PRIMING FOR FET CYCLES

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The worldwide shift towards frozen embryo transfer (FET) has accelerated, as the number of frozen embryos per patient for future use has increased dramatically. Better incubators, refined vitrification techniques which has improved the survival rate and quality of thawed embryos are few key features for this shift. The indications for embryo freezing for future use were extended beyond patients with suspected ovarian hyper stimulation syndrome and contributed to the increase in FET cycles and enable optimal Assisted Reproductive Technologies (ART) results in these cases

When one thaws an embryo, and transfers it to a primed uterus, which was made and frozen in an earlier treatment cycle it is called a FET (Frozen embryo transfer) cycle. Similarly, few women undergo oocyte donation cycles where fresh embryo/embryos are transferred. Both of these situations require endometrium priming with estrogen and progestogen in different doses and routes of administration.

Adequate embryo implantation is determined by good endometrial preparation and endometrial-embryo synchrony. For this preparation estrogen is crucial and different exogenous administration patterns could imply variations on endometrial priming. As, estrogen undergoes metabolization by the intestines and liver when administered orally, while, that is bypassed by transdermal administration. Similarly, Information on the effect of various oral preparations and route of administration of Estrogen on reproductive outcomes of women undergoing FET cycle is scarce.

There are three types of estrogen available in the market, these are 1) estradiol Valerate 2) 17-beta estradiol 3) conjugated equine estrogen

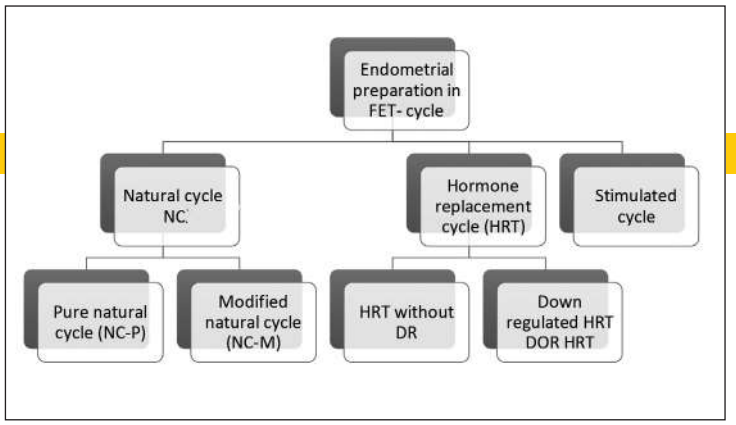
1) Estradiol Valerate is available as a prodrug and has to break before action. It undergoes extensive first pass metabolism so requires higher dose. It is also said to decrease intestinal metabolization of estradiol. When given in a dose of 2-4 gram, peak level is achieved within 3-6 hours.

2) Estradiol Hemihydrate or 17-Beta-estradiol is the hemihydrate form of estradiol, the most potent, naturally produced estrogen which is chemically and biologically identical to endogenous estradiol. Estradiol hemihydrate diffuses through the cell membrane and binds to and subsequently activates the nuclear estrogen receptor found in the reproductive tract, breast, pituitary, hypothalamus, liver, and bone. It is available for administration via different routes. The molecular formula for estradiol hemihydrate is C36H50O5

3) Conjugated equine estrogen- it is a mixture of estrone and equlin sulphate and exerts no effect until broken into two parts. Its absorbed slowly and causes biological variability and over load on liver.

Out of these three molecules Estradiol Valerate and 17-beta estradiol are being used for endometrial preparation in FET and donor-recipient IVF cycles. Our aim in this article was to focus on estradiol hemihydrate and its advantage over estradiol Valerate.

17-b Estradiol	Estradiol valerate	Conjugated equine estrogens
• Chemically and biologically identical to the endogenous human estradiol. • Unconjugated, hence rapidly available after ingestion. • Following oral administration and absorption, 17-β estradiol circulates in the plasma as "free" estradiol. • Due to the large surface of the microcrystals, a sufficient quantity of estradiol is absorbed rapidly.	• In the liver, estradiol valerate is split up rapidly into 17-β estradiol and valeric acid.3 • Compared with estradiol, slightly lower estrone levels are found, as valerate slows down the intestinal metabolization of estradiol. • Oral therapy is subjected to an extensive first pass metabolism.	• Mixture estrone and equilin sulfate (200 compounds). • No hormonal effect until after being split into the free steroid. • Increase the estrogen load on liver, thereby causing biological variability. • Relatively slow absorption of conjugated and unconjugated estrogens.



CONVERSION RATE OF DIFFERENT FORMULATIONS 1.0 mg of estradiol Valerate(oral/vaginal) = 0.75 mg of 17ß estradiol oral = 1.25 mg of 17 ß estradiol gel (transdermal)

The word estrogen priming is used in two different ways-

• When estrogen is being used in previous cycle to synchronize the follicular cohort before COS, e.g. poor responders.

• When estrogen is used to artificially prepare an endometrium in an HRT cycle either for FET or donor recipient cycles.

INDICATIONS OF FET CYCLE

• Hyper responders
• PCOS
• Where Pre-gestational genetic testing is required
• Personalized ET post ERA.
• Inadequate endometrial development
• Pre-mature follicular progesterone rise
• Fertility preservation
• Poor responders for embryo pooling
• Thin endometrium, fluid, polyp etc. on day of transfer
• Freeze for all

Oral estrogen administration is the preferred route as it is simple, easy, and effective. However, transdermal or parenteral route help in obtaining higher serum concentrations. The oral route of administration is well-tolerated. Oral estradiol is extensively metabolized by the intestinal mucosa and subsequently the liver.

WHY ENDOMETRIAL PRIMING IS NEEDED?

Optimal Endometrium Thickness Is Necessary for Embryo Implantation.

• Thick endometrium ensures receptive environment for embryo transfer and is a marker of endometrium receptivity.
• Endometrial thickness is strongest predictor of endometrial receptivity.
• Endometrial preparation increases receptivity for implantation and establishes pregnancy.
• Endometrium grows by the rate of 0.5 mm/day in proliferative phase; 0.1 mm/day in luteal phase.
• Right amount of estrogen and progesterone, during follicular and luteal phases, respectively, are crucial for endometrial cell proliferation.
• Endometrial thickness >9 mm gives significantly higher embryo implantation and clinical pregnancy rates as compared to endometrial thickness <7 mm.
• thin endometrium is less able to support implantation and pregnancy.

HOW DOES ENDOMETRIUM WORK?

• Causes spiral artery contraction
• Decreases oxygen tension in the functional layer
• Supports endometrial proliferation
• Induces sufficient progesterone receptors
• Induces endometrial receptivity
• Supports embryo implantation

TECHNIQUES FOR ENDOMETRIAL PREPARATION?

1) Natural cycle
2) Modified natural cycle
3) OI (ovulation –induction) cycles
4) Artificial cycles (hormonal replacement cycles)

• Down regulated HRT cycles
• HRT cycles without downregulation

This article is mainly focused on HRT cycles.

ARTIFICIAL OR HORMONAL REPLACEMENT CYCLES

1- Exogenous supply of estrogen & progesterone hormone is required to prepare the endometrium.
2- Initial estrogen priming is required for endometrial proliferation and the development of P4(progesterone) receptors.
3- Time bound secretory changes are brought by exogenous progesterone supplementation.
4- These cycles are easy to schedule and require minimal monitoring.

These cycles are done by completely downregulating the hypothalamic-pituitary-ovarian axis followed by artificial preparation of endometrium by exogenous estrogen in an increasing dose to simulate natural follicular phase. Once the endometrium crosses 8.00 mm progesterone is started. The duration of progesterone administration before embryo transfer is decided according to the embryo's age. Cleavage stage embryos are transferred after 4 days of progesterone and blastocysts are transferred after 6 days of progesterone administration.

In a recent Cochrane review done in 2020, where Thirty-one RCTs (5426 women) were included to study the outcome of various mode of endometrial preparation on endometrial thickness, implantation and clinical out come and they found that there is insufficient evidence on the use of any particular intervention for endometrial preparation in women undergoing fresh donor cycles and frozen embryo transfers. In frozen embryo transfers, low-quality evidence showed that clinical pregnancy rates may be improved in a stimulated cycle compared to a programmed one, and we are uncertain of the effect when comparing a programmed cycle to a natural cycle. Cycle cancellation rates are probably reduced in a natural cycle. Although administering a GnRH agonist, compared to without, may improve live birth rates, clinical pregnancy rates will probably be improved in a GnRH antagonist cycle over an agonist cycle. In fresh synchronized oocyte donor cycles, the clinical pregnancy rate is probably improved and cycle cancellation rates are probably reduced when starting progestogen, the day of or day after donor oocyte retrieval. Adequately powered studies are needed to evaluate each treatment more accurately.

OPTIMUM DAYS OF ESTROGEN STIMULATION

Various studies have proven that-

1) The optimal duration of estrogenic endometrial stimula-

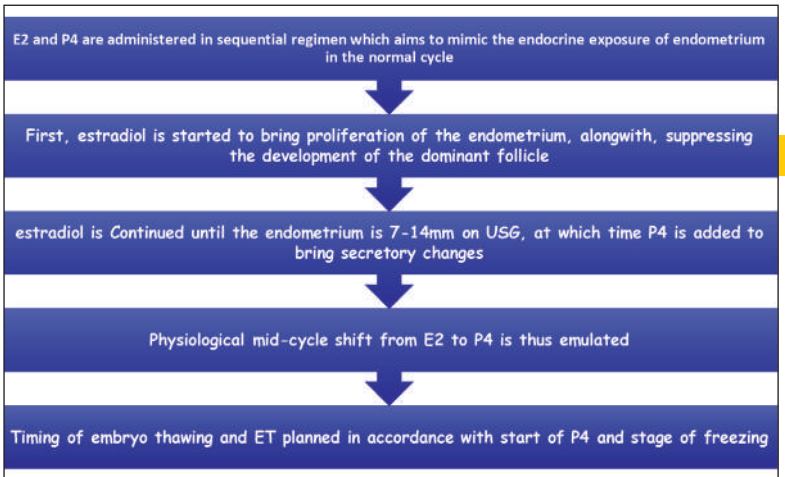


figure 1- Artificial estrogen priming in FET- without adding GnRH-Agonist

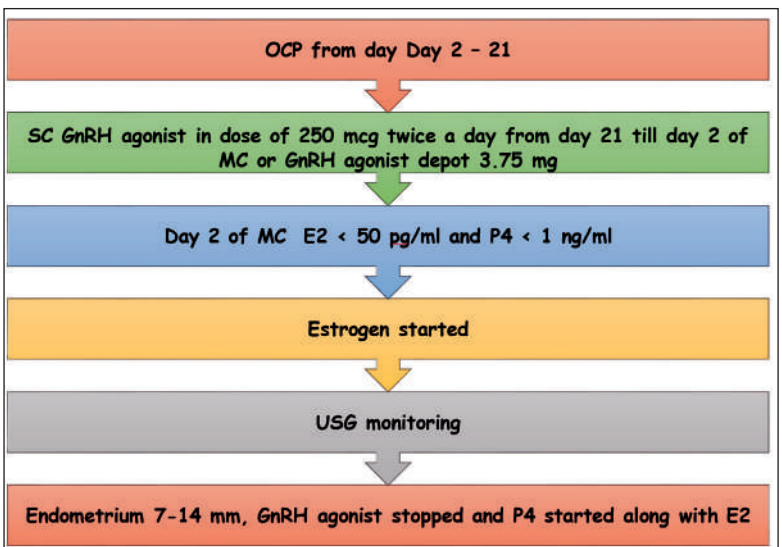


Figure 2- Artificial HRT cycle with GnRH-agonist

tion is 12– 19 days. But window of receptivity is tolerant to a wider range of E2 stimulation.
2) When a treatment lasts less than 12 days and more than 19 days, PR drops.
3) In a comparative study between long (21-35 days of E2 administration) and short protocol (6 days of E2 administration) and control group (14 days of E2 administration) done by Navot, Mid-luteal and late luteal endometrial biopsies were morphologically similar in each group, showing no detrimental effect of either short or long estradiol treatments. Progesterone addition seems to allow normal endometrial maturation regardless of the length of estradiol therapy but normal endometrial morphology does not always mean normal endometrial receptivity.
4) There is a high risk of abortion when E2 is given for very short time while break through bleedings are reported with very long E2 exposure, so, safe margin appears to be 11-40 days.
5) Studies show that a good pregnancy rate can be achieved either with short (<10days) or long (>40 days) E2 treatment. Above 40 days' implantation and pregnancy rates decrease a little but pregnancies are still possible beyond 60 days of estrogen stimulation. Maximum duration of E2 exposure reported is 76 days.

CONSTANT DOSE VERSUS FIXED REGIMEN OF E2 SUPPLEMENTATION

In fresh embryo transfer from oocyte donation cycles, changes in the protocol of E replacement do not seem to have an impact on clinical outcomes and performance; for this reason, estrogen replacement protocols can be adjusted to the patient's characteristics and preferences as well as to the most cost effective strategy.

IS THERE ANY DIFFERENCE IN OUTCOME AMONG VARIOUS E2 PREPARATIONS AVAILABLE IN THE MARKET?

Though there are not many randomized controlled studies to compare oral estradiol Valerate to hemihydrate but in a study done by Weigratz and colleagues Found that treatment with 2 mg micronized estradiol the serum concentrations are significantly higher than with 2 mg estradiol Valerate.
A latest study published by Ingle and colleagues in 2020, where they have compared implantation rate, clinical pregnancy rate and ongoing pregnancy rate after FET cycles between two groups of patients kept on estradiol hemihydrate and estradiol valerate. They found that estradiol hemihydrate group did not only do better in terms of endometrial thickness and vascularity (pi index) but also in implantation(87.7% vs 71.1%) and ongoing pregnancy rates(75.5% vs 60%).Though the clinical pregnancy rate was higher in Estradiol Hemihydrate group (75.5% vs 60%), it was not statistically significant (P=0.1074). There was no significant difference between biochemical pregnancy & miscarriage rate (10.2% vs 11.11%; P=0.8886, 12.24% vs 14.2%; P=0.7641) in both groups.
In another study where a total of 317 women with irregular menses and an-ovulatory cycle undergoing FET non-donor cycles without GnRH-a suppression were involved in a prospective randomized clinical trial where oral or transdermal estrogen was used for priming.
There was no significance difference in endometrial thickness, the day of progesterone administration, implantation rate, or, in clinical outcome between oral and transdermal estrogen group undergoing FET-Blast transfer without GnRH-a suppression.

CONCLUSION

Looking at the trend where most of the cycles are being done as "freeze all" the importance of endometrial preparation by estrogen is very instrumental as all the cycles can't be done as natural cycle. 17 beta estradiol (estradiol hemihydrate) being natural, mimicking ovarian estradiol and required in lesser dose seems to be a better choice for endometrial preparation in these FET cycles. Though literature is limited but whatever is available favors the use of hemihydrate in preference to any other molecule available as its giving better implantation and ongoing pregnancy rates. However more RCTs are needed to establish this benefit.

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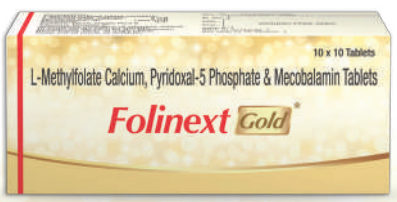

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Dr Chaitanya B Nagori
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LUTEAL PHASE SUPPORT IN ART

REAPPRAISING THE ROLE OF VAGINAL PROGESTERONE

Nearly 5 million babies resulting from assisted conception (in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI)) have been delivered, and the demand for these fertility treatments is increasing . Meticulous ovarian stimulation and well-programmed luteal phase support (LPS) are the foundation of treatment success. Luteal phase plays a crucial role in the development of a pregnancy preparing the endometrium for the blastocyst implantation. However, assisted reproductive technology cycles are known to have an insufficient luteal phase, probably due to the supra-physiologic oestrogen levels in IVF and ICSI in the follicular phase, as a result of ovarian stimulation used to prepare for oocyte 8retrieval. Therefore, sufficient luteal phase support (LPS) is essential during these cycles to improve implantation and pregnancy rates.

While the use of LPS following IVF/ intracytoplasmic sperm injection (ICSI) is widely accepted, and progesterone (P) is strongly recommended as its major constituent, there is no standard available regarding the formulation and route of administration, or on the timing and treatment duration .

Gaurdo and colleagues compared evidence-based practices with real life practices for luteal phase support in IVF. They showed that progesterone support is usually started on the day of oocyte retrieval and 80% of clinicians used vaginal progesterone only, while Intramuscular progesterone was prescribed by 6% and oral or SC progestin were each prescribed by 5% of clinician .

Recently published Delphi consensus (2021) evaluated global expert opinions on key aspects of assisted reproductive technology (ART) treatment. The evaluation showed that vaginal progesterone therapy represents the gold standard for luteal-phase support.

CLINICAL EVIDENCE

A 10-year follow-up on the practice of luteal phase support using worldwide web-based surveys by Shoham G and colleagues showed that vaginal route has always been the preferred route of administration. Over the years, they noticed a gradual increase in the use of vaginal P for LPS, at the expense of IM-P administration frequency, which decreased concomitantly.

Fatemi et.al explored the endometrial histology and endocrine profiles on day 21 of an artificial cycle in 6 women with premature ovarian failure (POF) treated with oral dydrogesterone (DG) or vaginal micronized progesterone. After estrogen endometrial priming, patients were randomized to receive DG or progesterone in two subsequent cycles. The main outcome measure was the endometrial histology and the endocrine profiles on day 21 of the cycle.

Results showed that the development of endometrial glands corresponded to an early secretory phase in five out of six cases supplemented with oral DG (out-phase). In contrast, five out of six cases treated with vaginal micronized progesterone showed an endometrium corresponding to a mid-luteal phase (in-phase) (P = 0.021 versus DG).

Overall, it was concluded that after estrogen endometrial priming in POF patients, exogenous vaginal micronized progesterone is more effective than oral DG in creating an 'in-phase' secretory endometrium and induces significantly higher progesterone and lower LH and FSH

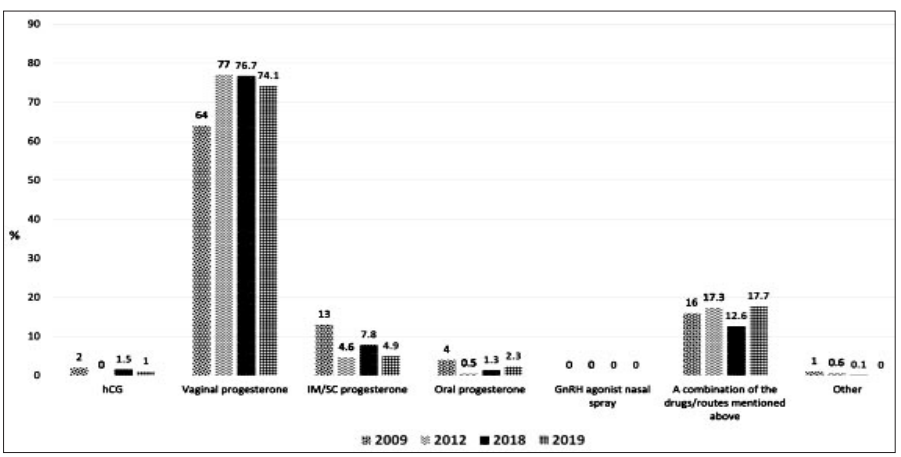
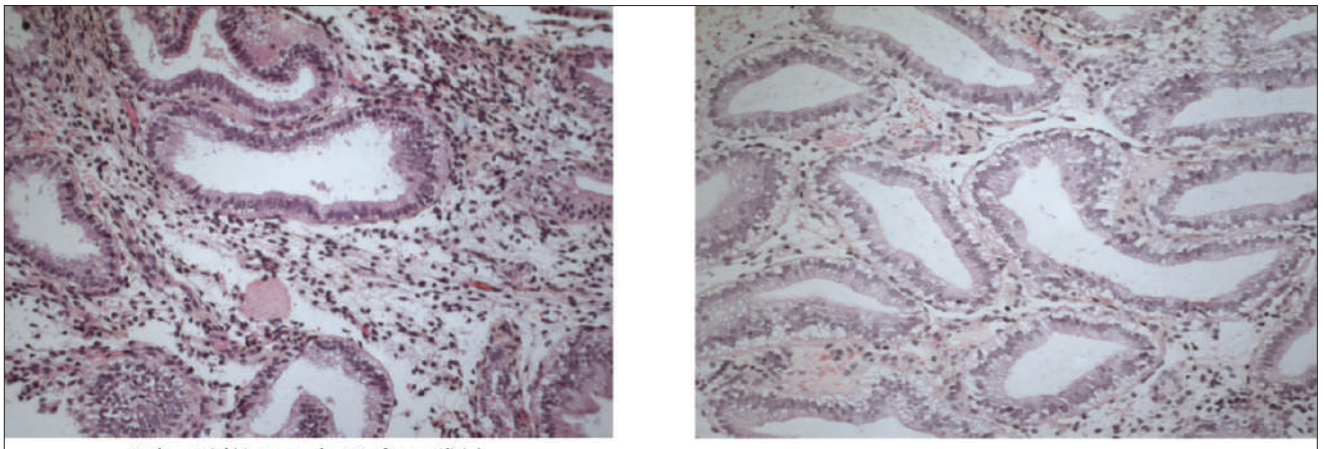


Figure 1: Responses to the survey question: what is your treatment agent/route of choice to support the luteal phase?



Endometrial biopsy on day 21 of an artificial cycle after micronized progesterone. Patients with premature ovarian failure received estrogen from days 1 to 21 and vaginal progesterone from days 15 to 21. (Coiled glands with active secretion and minimal residual vacuoles. Stromal oedema.) Absence of mitotic activity. The maturation corresponds to day 6 of the luteal phase

Endometrial biopsy on day 21 of an artificial cycle after oral dydrogesterone. Small glands with minimal coiling and persistant homogeneous subnuclear vacuoles and pseudostratified nuclei. (No stromal edema. Focal mitotic activity.) The maturation corresponds to days 2–3 of the luteal phase

Figure 2: Representative endometrial biopsy

serum concentrations on day 21 of the cycle.
A study by Saunders et.al published in 2020, evaluated the non-inferiority of vaginal pessaries (400mg) to vaginal gel (90mg) in 769 women undergoing in vitro fertilisation (IVF). In full analysis, clinical pregnancy rates on D38 were 38.3% for progesterone vaginal pessaries and 39.9% for progesterone vaginal gel. Further they concluded that progesterone 400 mg pessaries bid for luteal phase support is an effective, safe and tolerable treatment option for women undergoing IVF during ART .
A systemic review and meta-analysis of RCTs by Abdelhakim, et.al published in 2020, showed that vaginal progesterone is similar to intramuscular pogesterone in clinical pregnancy, ongoing pregnancy, miscarriage, and live birth rates. It was also associated with more satisfaction compared to intramuscular progesterone. It also mentions that vaginal progesterone has similar efficacy even in frozen embryo transfer cycles too, which is important as frozen cycle lacks the endogenous progesterone secretion due to the absence of functional corpus luteum, and it almost depends on the externally provided hormones for endometrial preparation.

IN FROZEN EMBRYO TRANSFER

In contrast to Fresh-ET, the absence of endogenous serum progesterone (P4) secretion before frozen embryo transfer in hormone replacement therapy cycles (HRT-FET) results in the need for exogenous progesterone formulations at approximately pregnancy weeks 8 to 10.
Recently published study by Bu, et.al (2019), evaluated the impact of endometrial thickness change after progesterone administration on pregnancy outcome in patients transferred with single frozen-thawed blastocyst. The results showed dynamic change of endometrial thickness after progesterone administration in FET cycles. An increased endometrium after progesterone administration was associated with better pregnancy outcome. Interestingly, clinical pregnancy outcomes and the increasing rate of endometrium were positively correlated .
A study by Jiang Lei published in 2019 compared vaginal progesterone vs. intramuscular progesterone in 3013 patients undergoing artificial cycle for frozen-thawed embryo transfer. Results showed that vaginal progesterone supplementation had significantly ($P < 0.05$) greater implantation (37.0% vs 34.4%), delivery (45.1% vs. 41.0%) and live birth (45.0% vs. 40.8%) rate than intramuscular progesterone injection.

CONCLUSION

Advances in ART have made a huge impact on humankind around the globe. Over the last four decades, we have seen major advances and breakthroughs in the individualization of controlled ovarian stimulation and in laboratory techniques. The choice of drug is dependent upon the patient characteristics and type of ongoing treatment. Most commonly used drug for LPS is vaginal progesterone which has favourable safety profile, efficacious, and feasible followed by intramuscular and aqueous progesterone.

BRINGING SMILES TO MILLIONS OF COUPLES

Dr Amit Bhatnagar
Country General Manager & Director
Origio India Pvt Ltd - A CooperSurgical Company

IVF and test tube babies – two words that always used to excite me as helping a couple to have a child is the most noble profession. When I heard IVF during my studies it was unbelievable that life could be created in a test tube, however slowly it became a reality with many of our friends and colleagues opting for IVF. I joined CooperSurgical in 2016 and ever since have been in awe of this wonderful ART industry. Having worked for more than two decades in varied fields of the medical device & diagnostics industry, while there has always been a sense of purpose in doing something meaningful that contributes to a healthier world, nothing can beat the joy of bringing smiles to millions of couples through what we do at CooperSurgical.

Elon Musk once said "Constantly think about how you could be doing things better and keep questioning yourself" and this is the philosophy I have always lived by and has been the driving force behind whatever we have been able to achieve as an organization in bringing smiles to millions of families and couples. When I joined CooperSurgical, my main aim was to be a knowledge and academic partner to our customers and the IVF fraternity and not just a vendor, and that is our vision in all our endeavors. One thing I have understood and feel makes a huge difference is the commitment towards being better

and providing customers with solutions beyond products, winning the trust of people you work with and supporting the fraternity in advancing the world of IVF.

The Origio brand of ART products were available in India through an erstwhile distributor since 1995 serving the Indian ART fraternity. However, eventually Origio decided to come direct in India and acquired major stakes in 2012 &d 2013, completing the final acquisition in 2015 with a dedicated organization for sales, service, marketing & logistics and an aim to provide services beyond products, establishing a Centre of excellence for teaching & training and a dedicated infrastructure for serving our customers better to continue the legacy of Origio along with other CooperSurgical brands in India.

With trusted brands older than 4 decades in the field of ART, CooperSurgical was established with a vision of healthy family, women, and babies and with a mission to find & deliver solutions that can make a positive impact and improve healthcare. The foundation on which CooperSurgical stands today are the four pillars of CooperSurgical: Ethical, Passionate, Innovative and Respectful and each of our associates stand by these 4 pillars.

For the last four years, my endeavor has been to provide our customers with the best experience in terms of quality, reliability & service of our products and trust through our associates. I am indebted to the entire fraternity for accepting me and my CooperSurgical family and giving us the opportunity to be their partners, not just inside the lab but also for various knowledge sharing initiatives like CMEs, journal clubs, panel discussions, trainings and workshops and not to forget the first time ever consensus guidelines with ISAR, ACE and IFS, a breakthrough in the Indian IVF industry.
In these last 4 years, we have ensured that we keep raising our bar and increase our reach through our direct team

and channel partners to serve customers throughout India with ease and proper storage & quality; bringing newer initiatives and platforms for knowledge sharing so that we grow with the fraternity and help in bringing standardization and global expertise through our global medical affairs and innovation team in India as well.
I still remember the first training and roadshow that we did and what a journey it has been since then. The kind of support we have received from ISAR, ACE and IFS is commendable. I am thankful to the entire 'ART' family for the support and encouragement, and for keeping our spirits high. We keep striving to become better and better with each passing year with your support and feedback. Right from the global team to every single associate in the Indian team we are driven by the same passion, and with our products & expertise, always attempt to bring in the best global solutions through the suggestions and guidance of you all.
I feel proud of being in this industry and contributing to a noble cause. I still remember the first time I shared with my children about where I work and what I do, the smile that came to their faces and how proud they felt to learn about what I do. This ART family has given us a purpose of bringing smiles to millions of couples and each day we start with the commitment to be better than before.

LASERS IN ART

Dr Sujatha Ramakrishnan
PhD, Nova IVF Fertility Group

Dr MS Srinivas
MSSC, PhD
Vice Chairman, Embryology ISAR

LASER, an acronym for light amplification by stimulated emission of radiation, was first demonstrated in 1960 and since then has been tried for possible application in the medical field. Basic action of laser is mediated through removal or direct breakage of molecular bonds of the tissue by high energy radiation in a very precise and clean manner without much of thermal damage. Laser usage in IVF has replaced mechanical and chemical manipulation, thereby increasing efficiency, accuracy, and reducing inter-user variability.

TYPES OF LASER

Basic components of a LASER system involve an energy source, gain medium or laser medium and two or more mirrors that form an optical feedback. Wavelength of operation and other properties of the laser are determined by the laser medium, which is made of solid (sapphire (Al2O3), neodymium-doped yttrium aluminum garnet (Nd:YAG), liquid (dyes), gas (Helium, Neon, Argon) or semiconductor materials (InGaP {indium gallium phosphide}). Common energy sources used are electrical, light or chemical reactions. Lasers can further be divided into contact and non-contact lasers. In contact laser there is a direct contact between the laser and the sample through an optical or glass fiber which also requires special media other than the routine culture media for efficient energy transfer. In non-contact laser, beams are directed through objective of an inverted microscope along its optical axis avoiding direct contact with the sample thereby overcoming contamination and mutagenicity previously reported with contact laser.

Nd:YAG laser (1064 nm) was the first non-contact laser used in IVF. Argon fluoride (ArF), xenon chloride (XeCl), krypton fluoride (KrF), nitrogen and Nd:YAG lasers were few other first generation lasers and most of them function in the UV spectrum. Since UV wavelengths are closer to the absorption of DNA, which is known to cause mutagenic effects, efforts were made to design lasers in the infrared region (>800nm). Erbium:yttrium-aluminum-garnet laser (Er:YAG), Holmium:yttrium-scandium-gallium-garnet laser (Ho:YSGG) are second generation lasers in the infrared region. Indium-gallium-arsenic-phosphorus (InGaAsP) semiconductor laser at 1.48 um diode wavelength, which is demonstrated to be safe for gametes and embryos, giving consistent results in the form of uniform, smooth edged tunnels is the laser currently used in IVF. Three characteristics of laser, which directly impact embryos are wavelength, power, and pulse length which in turn determines number of shots required and irradiation time. Shorter the exposure time and power, lesser is the thermal effect on the gametes and embryos.

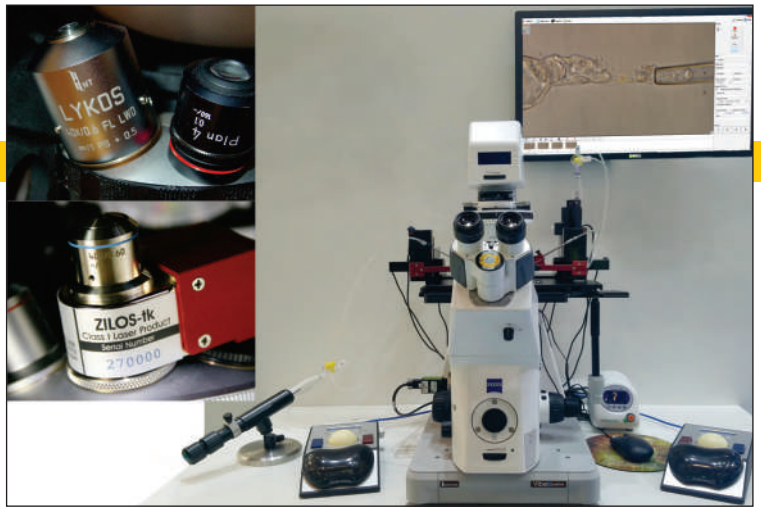
APPLICATION OF LASERS IN IVF

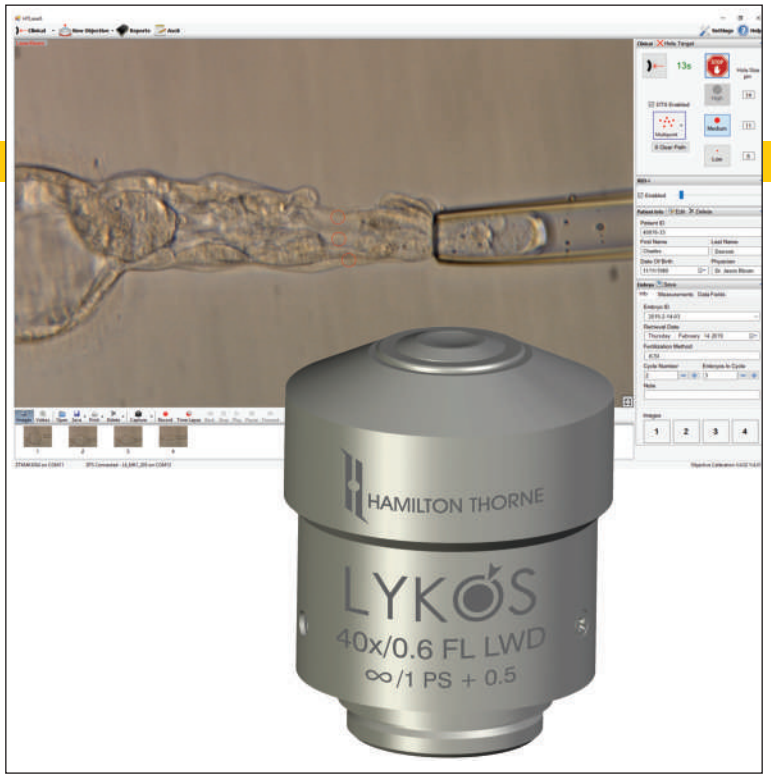
Oocytes

Nd: YAG laser at 1064 or 534 nM and tunable ti Sapphire laser at 650 - 1080 nM were used for zona pellucida ablation in oocytes, either for thinning of zona or creating a complete breach to aid in fertilization in severe male factor infertility. Low power Helium-Neon laser has also been used for triggering maturation in immature oocytes. Radiation at doses of 2, 4, 8 and 16 J/cm is shown to stimulate acrosome reaction which was comparable or or even better than chemical agents such as caffeine, calcium, and heparin. Lasers have also been used in the preparation of zona for the hemizona assay, a diagnostic tool and a research model to assess the binding capacity of sperm to the oocyte zona and to study the effects of the environment or administered medications on the zona pellucida respectively.

Sperm

In a couple with male primary cilia dyskinesis, where the semen sample showed curled flagella and immotile spermatozoa, viable sperm was detected using 1.48 micrometre diode identified by a twitching motion on exposure to laser. Identified viable spermatozoa were injected into oocytes and transfer of resultant embryos resulted in a singleton pregnancy. Similarly, low power laser irradiation is also shown to stimulate sperm motility which is mediated through ATP production. Helium-Neon laser clearly enhanced human sperm motility as well as velocity. Improved fertilization using irradiated spermatozoa was also reported by biochemical





and topological analysis in human samples. Long term storage of spermatozoa in liquid nitrogen is known to result in deterioration of sperm quality which is shown to be overcome by laser irradiation. Though the mechanism of such reactions is not completely elucidated, it is proposed that laser activation of sperm motility is mediated through respiratory chain molecules which can act as photo receptors.

Embryos

Implantation capacity of human embryos is compromised due to many factors like increased maternal age, poor gamete quality and in vitro culture conditions. Assisted hatching, a procedure by which the zona pellucida of an embryo is manipulated, is a method helpful if implantation failure is due to the inability of the embryo to hatch out of the zona. In advanced maternal age and in frozen embryo transfer cycles, assisted hatching is shown to result in better implantation rates. Laser induced hatching is also widely applied in embryo biopsy procedures for genetic testing. Compared to mechanical and chemical hatching, laser drilling enhances the recovery of intact blastomeres and trophectoderm cells post biopsy, with an added advantage of minimal time requirement for the procedure. Laser induced hatching is also applied in blastocoele collapse before vitrification and removal of necrotic blastomere from embryos, procedures which have been shown to result in better IVF outcomes.

SAFETY

Lasers which are approved for clinical use in ART are Zilos-tk, LYKOS, Saturn 5 and Saturn 5 active. Zilos tk and LYKOS operate at 1460 uM wavelength, 300 MW power and 1 microsecond pulse length. Laser is built into 40 X objective and is the only portable laser in the market. Saturn 5, a movable laser operates at 1480 uM wavelength, 400MW power, pulse lengths ranging from 5-2000 microseconds and works through 40X and 20X objective. Choice of laser depends on the intended application in IVF lab as peak temperature, thermal spread and exposure temperature might affect the gametes and embryos. At present it is reassuring that several studies have proven the safety of laser. No increase in congenital malformations after laser hatching was reported in a follow up study of 134 children. However Chailer et al demonstrated lower trophectoderm cell numbers in laser assisted hatching embryos compared to controls. More robust evidence on pregnancy outcome and in depth analysis of laser settings is needed for optimization of usage of laser in IVF and also to prevent possible epigenetic modifications.

CONGRATULATIONS ON YOUR ACHIEVEMENTS

ISAR MEMBERS' ACHIEVEMENTS 2020-2021

Dr Madhuri Patil

Appointments:

a. Editorial board 2020-2021- Endocrinology an official journal of "The Endocrinology Society" USA

b. Executive Member of Asian Society for Fertility Preservation (ASFP) 2021-2022

c. Chairperson ASPIRE SIG Reproductive Endocrinology including PCOS 2021 – 2023

d. Speciality Editor for Fertility and Sterility

Publications:

a. Installing oncofertility programs for common cancers in limited resource settings (Repro-Can-OPEN Study): An extrapolation during the global crisis of Coronavirus (COVID-19) pandemic. Journal of Assisted Reproduction and Genetics (2020) 37:1567–1577.

b. Endocrine and Metabolic aspects of tuberculosis. US Endocrinology 2020;16(2):88–96.

Dr Manish Banker

Publications:

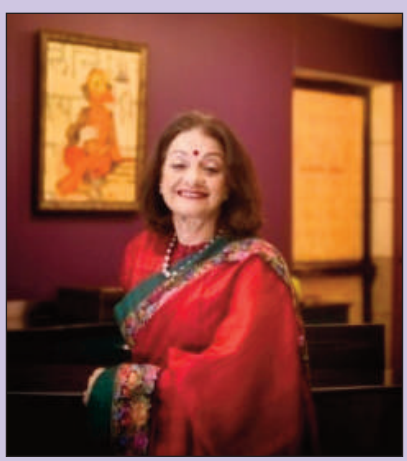
a. International Committee for Monitoring Assisted Reproductive Technologies world report: assisted reproductive technology 2012. Hum Reprod. 2020 Aug 1;35(8):1900-1913.de Mouzon J, Chambers GM, Zegers-Hochschild F, Mansour R, Ishihara O, Banker M, Dyer S, Kupka M, Adamson GD.

b. The influence of delayed blastocyst development on the outcome of frozen-thawed transfer of euploid and untested embryos. J Hum Reprod Sci; 2020;13:155-61; Sardana P, Banker J, Gupta R, Kotdawala A, Lalitkumar P G, Banker M.

c. ART utilization: an indicator of access to infertility care. Reprod Biomed Online. 2020; S1472-6483 (20) 30137-1; Dyer S, Chambers GM, Adamson GD, Banker M, De Mouzon J, Ishihara O et al

d. Maternal and neonatal complications in twin deliveries as compared to singleton deliveries following In vitro fertilization. J Hum Reprod Sci 2020; 13:56-64; Gupta R, Sardana P, Arora P, Banker J, Shah S, Banker M.

Dr Duru Shah



Appointments:

a. Representative: PCOS Society of India to the Federation of Societies of International Societies of Gynecological Endocrinology (FISGE) 2017 onwards

b. Invited to Chair: Special Interest Group (SIG) on "Reproductive Endocrinology & PCOS", Asia Pacific Initiative on Reproduction (ASPIRE) 2018 - 2021.

c. International Advisor: Special Interest Group (SIG) "Safety & Quality in ART" (SQART), European Society of Human Reproduction & Embryology (ESHRE) 2019 onwards.

d. Invited on the Board of the Asia Pacific Initiative on Reproduction (ASPIRE) 2021-2023.

e. Invited Member: International Advisory Panel: Centre for Research Excellence in Polycystic Ovary Syndrome. (CRE-PCOS), 2017 onwards.

Publication:

a. Infertility management in lean v/s obese PCOS. Frontiers in Gynecological Endocrinology. June 2020

Dr Pramod Krishnappa

Award:

Awarded "Millennium International Urology Conference (MIUC) Travelling Fellowship 2020" by Association of Southern Urologists (ASU) scheduled at the Andrology unit at University College London Hospitals, (UCLH) under Prof Dr David Ralph in 2021.

Publications:

a. Cadaveric Penile Prosthesis Workshop training improves surgical confidence levels of urologists: South Asian Society for Sexual Medicine course survey. Int J Urol 2020 Nov;27(11):1032-1037. Krishnappa P, Srini VS, Shah R, Lentz AC, Garaffa G, Martinez-Salamanca JI, Moncada I.

b. Prevalence, assessment and surgical correction of penile curvature in hypospadias patients treated at one European Referral Center: Description of the technique and surgical outcomes. World J Urol 2020 Aug;38(8):2041-2048. Bandini M, Sekulovic S ,Spiridonescu B, Krishnappa P, Dangi AD , Slavkovic M , Pesic V , Salonia A , Briganti A , Montorsi F, Djinovic R.

Dr Keshav Malhotra

Appointments:

a. Co-chair, Embryology for ASPIRE 2021

b. Selected as Mentor for ESHRE-funded traveling Fellowship in 2021

c. Invited by ESHRE as Expert for Journal Club in March 2021

Dr Rutvij Dalal

Publication:

Artificial Intelligence in Assisted Reproductive Technology: Present and Future. Int J Infertil Fetal Med 2020;11(3):61-64. Dalal RJ, Gupta S, Mishra AP.

Dr Ashish Kale

Publication:

Comparison of Clinical Pregnancy Rates and Implantation Rates in Hysteroscopic Lateral Metroplasty versus Endometrial Scratching in Patients of Repeated Implantation Failures. J South Asian Feder Obs Gynae 2020; 12 (6):348-352. Kale A, Kale A.

Dr Neha Singh

Publications:

a. Standardized Laboratory Procedures, Quality Control and Quality Assurance Are Key Requirements for Accurate Semen Analysis in the Evaluation of Infertile Male. World J Mens Health. 2021;39:e20. Agarwal A, Sharma R, Gupta S, Finelli R, Parekh N, Selvam MK, Pompeu CP, Madani S, Belo A, Darbandi M, Singh N, Darbandi S, Covarrubias S, Sadeghi R, Arafa M, Majzoub A, Caraballo M, Giroski A, McNulty K, Durairajanayagam D, Henkel R.

b. The effect of paternal age on intra-cytoplasmic sperm injection outcome in unexplained infertility. Arab Journal of Urology. 2021. Haitham Elbardisi, Mohamed Arafa, Neha Singh, Bridget Betts, Ashok Agarwal, Ralf Henkel, Alia A Al-Hadi, Hasan Burjaq, Kareim Khalafalla, Ahmed Majzoub.

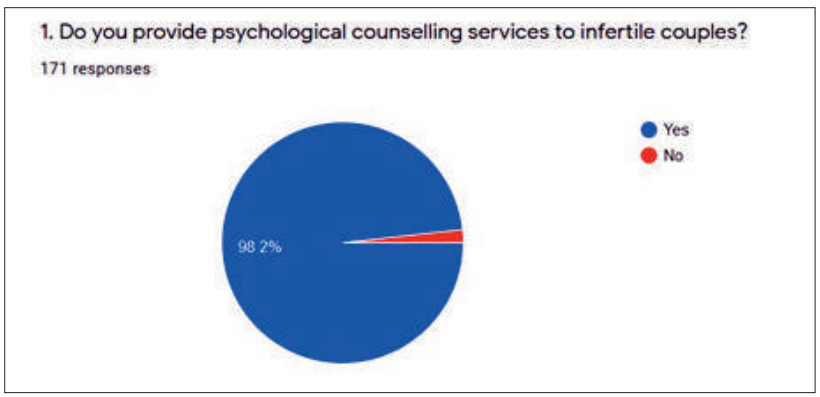
c. Published an article "The clock is ticking away-Covid-19 and infertile patients" in UK's Swasthya Health Journal in August 2020 issue2, volume1.

Dr Sulbha Arora
Editor & Member Executive Committee, ISAR

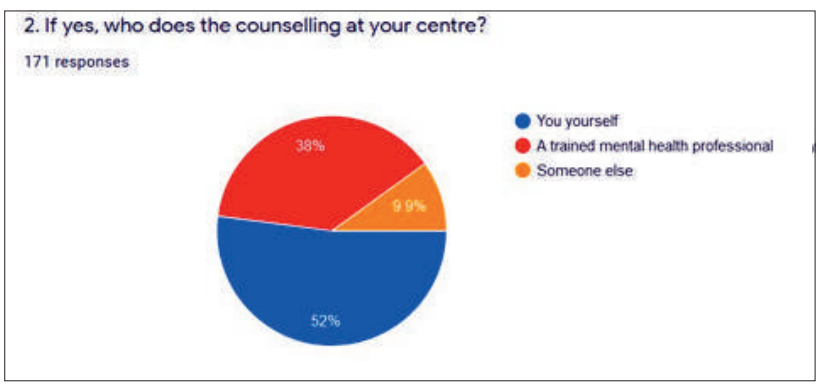
ISAR SURVEY ON STRESS & COUNSELLING

AN ANALYSIS

A survey regarding the psychological stress faced by infertility patients and the counselling provided to them was conducted among Indian practitioners. 171 clinicians participated in this survey. The responses obtained are elaborated below, along with a corresponding discussion for each question based on available published guidelines.

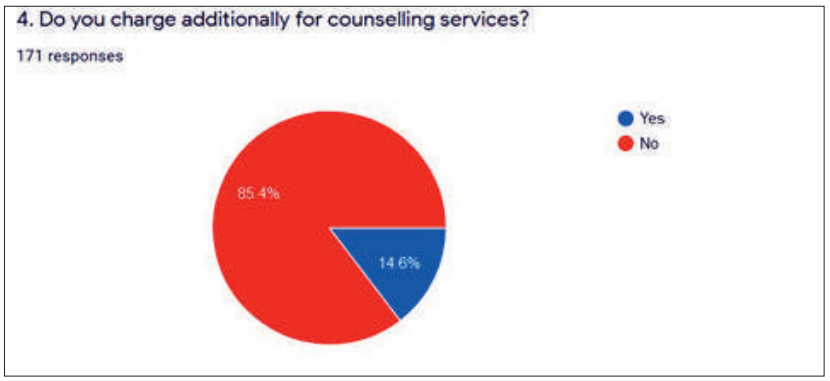


ANSWER -1
98% responded with a 'yes' when asked whether they provide counselling services to their patients. As per the ESHRE Guidelines on Counselling in Infertility, in addition to the necessary medical procedures, one should also focus on the patients' psychological and emotional needs.

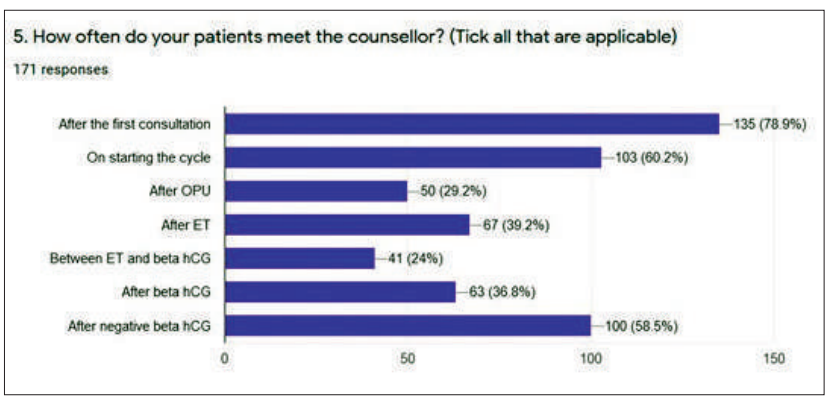


ANSWER – 2
The majority of the clinicians responded that they do the counselling themselves. As per the ICMR Guidelines, Counsellors are an important adjunct to any fertility clinic. A person who has at least a degree (and preferably a post graduate degree) in Social Sciences, Psychology, Life Sciences or Medicine, and a good knowledge of the various causes of infertility and its social & gender implications, and the possibilities offered by the different treatment modalities, should be considered qualified to occupy this position.

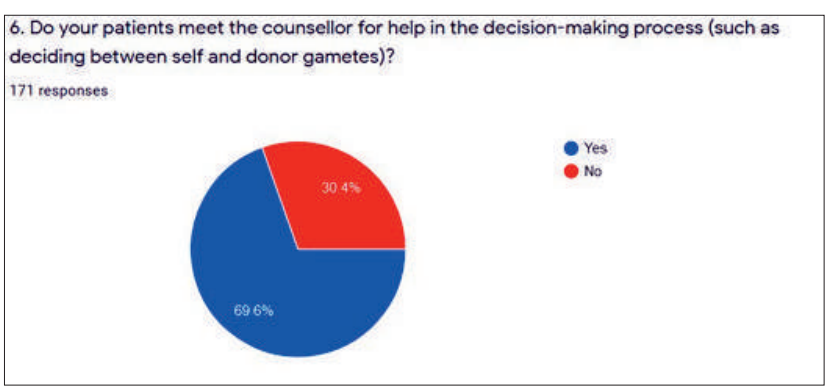
ANSWER-3
As per the ESHRE Guidelines, caring for the emotional needs of patients demands continuity and should not be treated as a single event. A member of the staff of an ART clinic who is not engaged in any other full-time activity in the clinic can act as a counsellor.



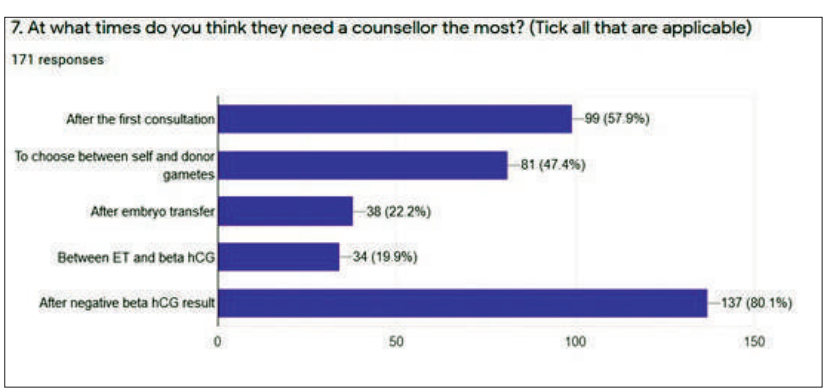
ANSWER-4
There are various methods of incorporating counselling into medical treatment and this also affects payment for the counselling service. If the counselling service is included in the treatment fee, it is most likely to facilitate access for a high number of patients. On the other hand, it makes treatment more expensive for those patients who do not take advantage of the counselling service. More than 85% of clinicians responded that they do not levy additional charges for counselling.



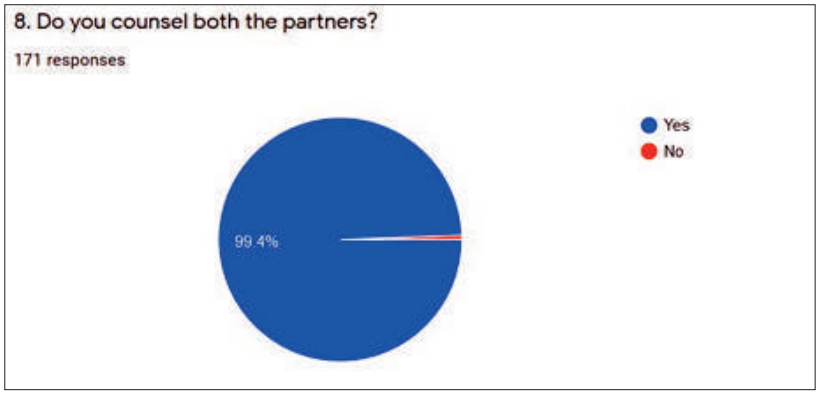
ANSWER-5
The counsellor is required to understand the stages of the treatment and the kind of emotions associated with the same. Good awareness of the stage and being sensitive & empathetic will help in doing the right counselling at the right time.



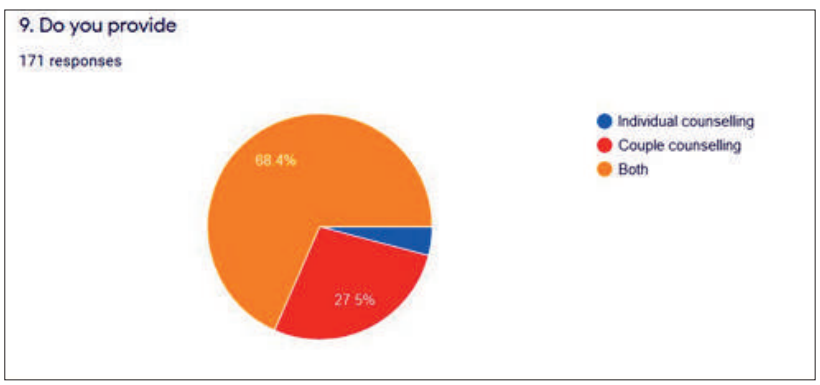
ANSWER-6
One of the important concerns that the patient may experience is of accepting the treatment advised. They may have myths, misconceptions and preformed false notions regarding many aspects of ART. The counsellor needs to explain the need and the reason for the treatment options that have been offered, along with the legal implications involved, and thus help them to take an informed decision by clarifying doubts, busting myths, and providing supportive and implication counselling.



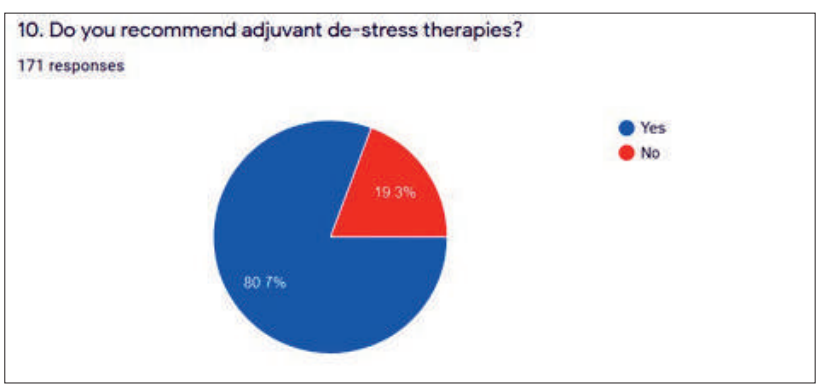
ANSWER-7
The need for psychological counselling can majorly be divided into three stages: Before, during and after treatment. The stages to be considered during the treatment are day of starting stimulation, day of follicle scan (as treatment may be continued or cancelled on this day based on response), day of OPU and day of ET. After treatment stages include the waiting period post embryo transfer, the day of result, as well as dealing with miscarriages / ectopics.



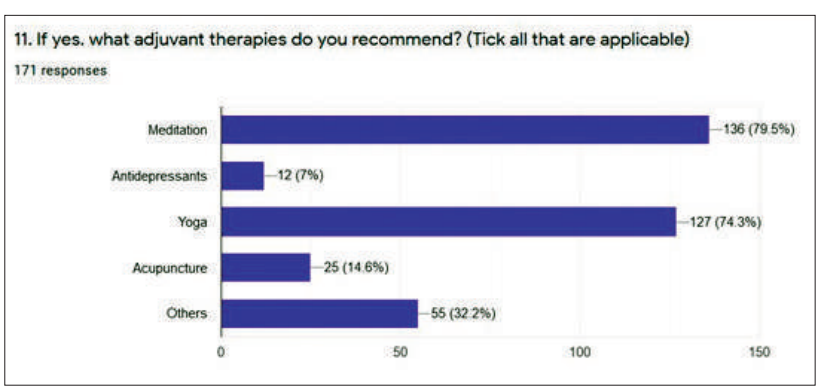
ANSWER-8
It is essential that infertility counsellors be aware of how men and women experience infertility differently. As per the ESHRE Special Interest Group of Psychology & Counselling, nearly all studies confirm that women experience greater amounts of infertility-related stress. Women are also more likely than men to report depression and anxiety symptoms, take a more active role in medical treatment, and respond more poorly following treatment failure. Men experience infertility stress, but appear less emotionally affected and are more willing to consider treatment termination.



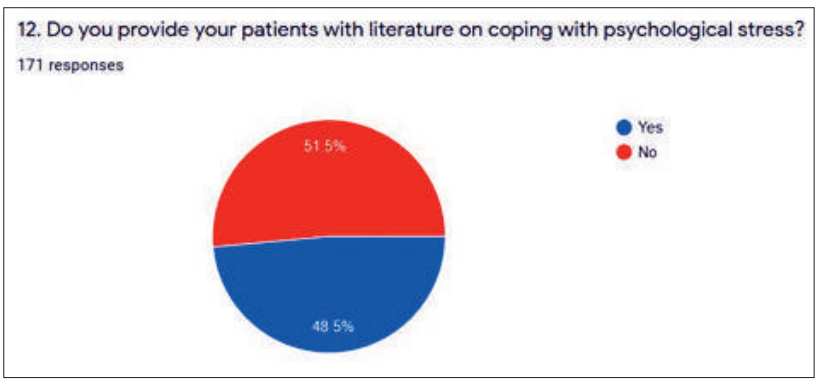
ANSWER- 9
With regard to counselling services, women have more positive attitudes towards seeking psychological help than men, and they are more likely to seek couple counselling for general distress. It is important to counsel both the partners together as well as individually. The couple's relationship dynamics, sexuality, ability to cope with the psychological and emotional effects caused by this process must be considered in addition to the course of treatment and future treatment options.



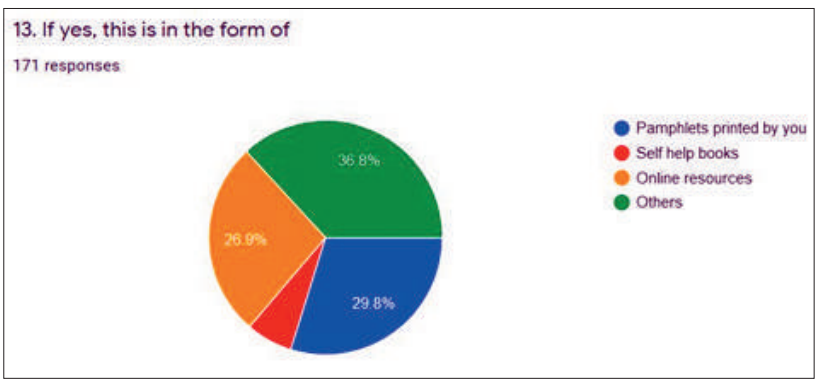
ANSWER-10
Given that infertility and its treatment often cause considerable stress, experts recommend various relaxation techniques. For example, mindfulness meditation, deep breathing, guided imagery, and yoga promote stress management. Over 80% clinicians replied that they do discuss adjuvant distress therapies to help their patients cope with stress.



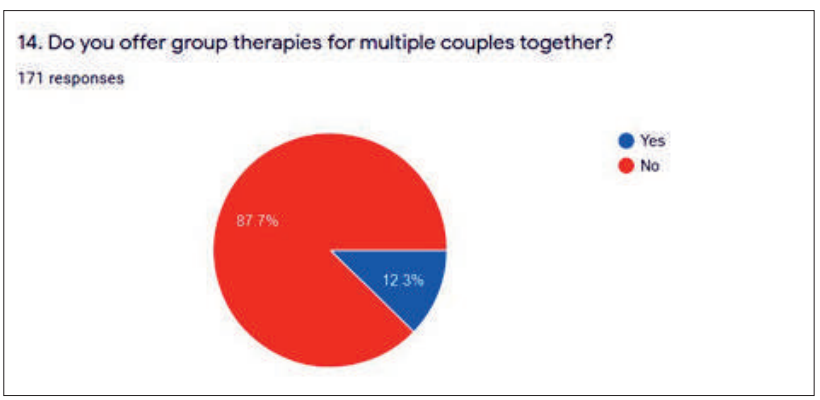
ANSWER- 11
The use of complementary and alternative medicine (CAM) is becoming increasingly popular in the United States. In countries like India and China, some of these techniques have been used for centuries. Most of the existing studies suggest that Acupuncture can improve the outcome of IVF-ET, and the mechanisms may be related to the increased uterine blood flow, inhibited uterine motility, and stress reduction. Yoga and meditation can help increase the clarity of the mind, maintain healthy body chemistry, and give patients the patience to undergo the rigors of infertility treatments.



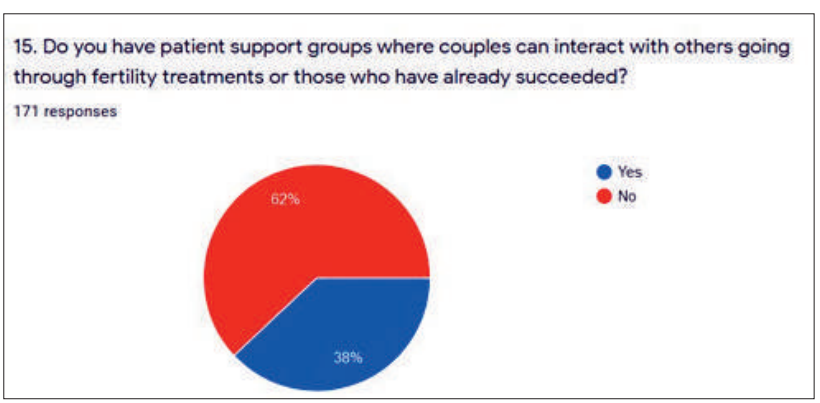
ANSWER - 12
According to the ESHRE Counselling in Infertility Guidelines, the most frequently provided adjunct services are written information and telephone counselling. The purpose of adjuncts is to ensure that an adequate amount of psychosocial information is available to all patients, including those who would not access such information through contact with clinic staff or specialised counsellors



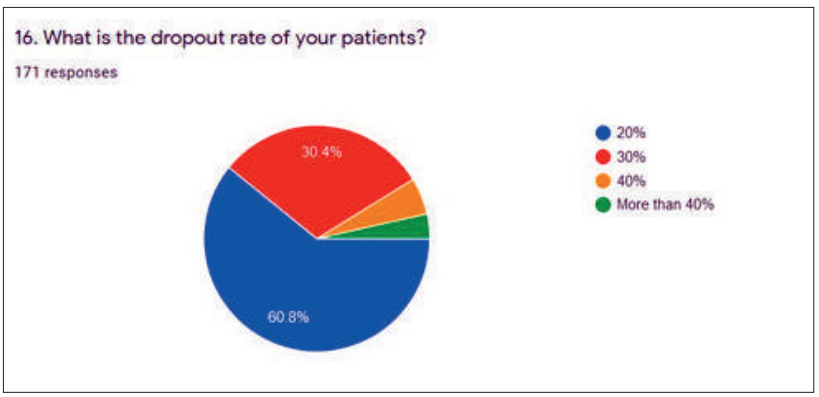
ANSWER- 13
Preparatory psychological information can be very concrete (e.g. step-by-step description of oocyte retrieval) or very abstract (e.g. description of feelings of loss), and can be provided in different formats (e.g. written, videotaped). Only a few studies have evaluated the effectiveness of written and/or videotaped information with infertile patients. Such information can be beneficial for patients, especially when the information is specific to ongoing experiences.



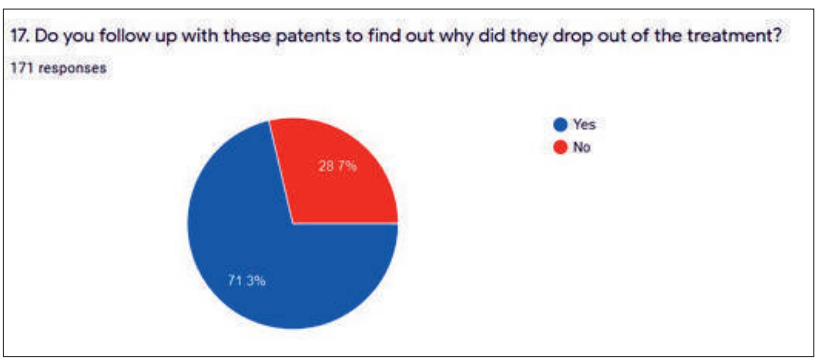
ANSWER-14
There are many therapeutic advantages unique to groups. Having the opportunity to be part of a group with members facing the similar problems, sharing painful and confusing issues, as well as feelings of stigmatisation (often in the case of treatment with donor egg, sperm or embryo) is considered a tremendous relief. In this sense, group work breaks down social isolation and has a normalising effect.



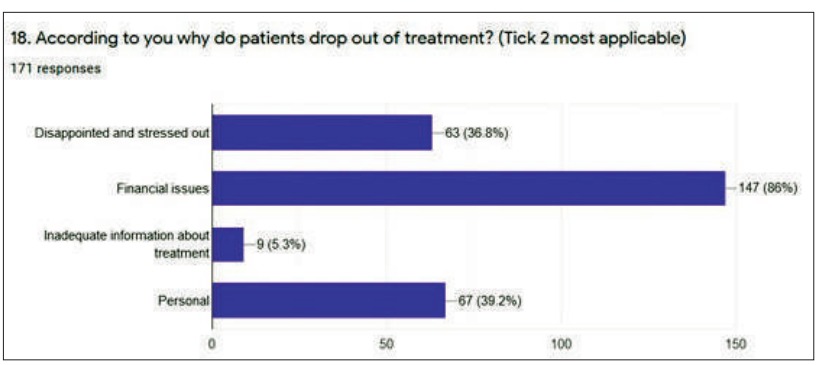
ANSWER- 15
The large majority have responded that they do not conduct support group meetings for their patients, and this seems to be an area that needs to be improved upon. Support group meetings provide a good opportunity for them to interact with others and find out how they coped with many of the same situations they themselves are facing.



ANSWER- 16
A study from UK reports a dropout rate ranging from 25-42%, increasing with subsequent cycles. Indian data is limited. In this survey, 90% of respondents replied that their dropout rates are 20-30%, which seem at par with those from other countries.



ANSWER- 17
There is continuous need to review the IVF program and have quality control. One of the ways to do this is to get the patients' feedback so the centre can learn where it needs to improve. Also, patients should be counselled in detail for long-term treatment and limitations of the procedures so they are prepared for multiple cycles if the first cycle fails to achieve pregnancy.



ANSWER- 18
As cost is a major factor in discontinuation, cost-reduction strategies should be evolved to reduce discontinuation. The other major cause of dropout in IVF is mainly related to stress. Reducing stress will improve compliance and decrease dropouts. Moreover, IVF should be made patient friendly and simplified. Efforts taken jointly by IVF clinics, society, government, industrial sector, and media can reduce dropout rates by providing education, cost reduction, psychological support, and quality control.

A Publication of Indian Society of Assisted Reproduction

Journal of Human Reproductive Sciences

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Scope of the Journal

The Journal of Human Reproductive Sciences covers all aspects of human reproduction - Andrology, Assisted Conception, Endocrinology, Physiology and Pathology of Implantation, Preimplantation Diagnosis, Preimplantation Genetic Diagnosis, Embryology & Ethical, Legal and Social Issues involved with infertility.

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INFERTILITY, L-METHYLFOLATE & MTHFR POLYMORPHISM- THE INVISIBLE THREAT

Padmashree Dr Shanti Roy
MBBS (Hons) Gold Medalist, DGO
MS, MNAMS, FICS, FICOG
Ex-Professor & Head: (Obs-Gyn, PMCH, Patna).
Padmashree Awardee-2020.

INTRODUCTION:
Folate deficiency can occur because dietary folate intake is low or because of the genetic defect, hampering folate metabolism, viz. methylenetetrahydrofolate reductase (MTHFR) polymorphism. The MTHFR is a critical enzyme in folate metabolism and is responsible for conversion of inactive folic acid into active L-5-methyltetrahydrofolate (L-5-MTHF), also called as 6[S]-5-methyltetrahydrofolate or L-Methylfolate.
The MTHFR directs folate species to homocysteine (Hcy) remethylation. The MTHFR polymorphism affects this activity of the MTHFR enzyme leading to hyperhomocysteinemia and is associated with various Infertility & pregnancy complications.
Global prevalence of MTHFR polymorphism ranges from 20 to 50%, whereas in India, it is between 28 and 35%. Such a high prevalence poses a great burden of functional folate deficiency and related complications. In such a condition, supplementation with the active form of folate, i.e., L-5-MTHF, is a better alternative to folic acid.

FOLIC ACID VS 5MTH F
Folic acid is a synthetic folate form enjoying good stability and cheap manufacturing but it is very rare in nature and does not naturally occur in humans. It is transformed into 5-methyl THF with the help of an intact MTHFR, B2 and B3 vitamins. 5-MTHF is the metabolically active form of folic acid obtained through a reductive process. 5-MTHF can like folic acid be formed.

HYPERHOMOCYSTEINEMIA AND MTHFR
Deficit in MTHFR activity may cause hyperhomocysteinemia and homocysteinuria with all their clinical manifestations including developmental delay, osteoporosis, thromboembolic and Cardiac diseases and premature atherosclerosis. It is associated with an increased risk of fetal open neural tubal defects. Serum homocysteine should be checked when there is MTHFR gene mutation, especially when dealing with a homozygous or compound heterozygous type. Homocysteine levels are typically higher in men than in women, and increase with age. Elevated levels if >10.4 µmol/L or >140 µg/dL (female) and if >11.4 µmol/L or >150 µg/dL (male).
The individuals who lack of the enzyme that metabolizes folic acid to its active form. Active form (5-MTHF) must be given, bypassing the defective enzyme, and providing the body with the final active product, as well as reducing the homocysteine levels. Individuals affected with MTHFR gene mutation must firstly modify their diet and decrease their intake of fortified wheat flour and folic acid supplements. Homozygous or compound heterozygous women who have experienced repeat fetal loss should be treated with active 5-MTHF (L-methylfolate) as well as taking low molecular weight heparin (LMWH) to counteract hypercoagulability due to potential hyperhomocysteinemia.

AUGMENTATING HYPERHOMOCYSTEINEMIA LOWERING ACTION OF L-5-MTHF WITH METHYLCOBALAMIN AND PYRIDOXINE
Apart from folic acid, vitamin B12 and vitamin B6 can also lower the homocysteine levels and augment this action of folic acid. Studies conducted by Bibi et al demonstrated that the combination of folic acid, vitamin B12, and vitamin B6 significantly lowers homocysteine levels in hyperhomocysteinemic women. Safety and tolerability of B vitamins are well established. Studies conducted by Maladkar et al1, demonstrated that the fixed dose combination of folic acid and methylcobalamin is effective and well tolerated in the treatment of patients with vitamin B deficiency. Thus, supplementation with 5-L-MTHF, vitamin B12, and vitamin B6 can act synergistically and effectively reduce homocysteine levels as compared with either of the vitamins alone.

GAMETES, EMBRYOS AND MTHFR
MTHFR isoform has a real negative impact on early embryonic development, directly driven by the maternal stores or reserves previously accumulated. The negative impact is also observed on the male gamete. Folate-receptor-1 and folate-transporter-member-1 are two of the most expressed mRNAs in the oocyte. Only portion of the ingested folates can be metabolized in carriers of MTHFR mutations and be used in the one-carbon-cycle (1-CC).
When comparing treatment with FA, 5-MTHF induces significantly higher plasma folate concentration irrespective of mutations of MTHFR.
HABITUAL ABORTIONS AND MTHFR
In patients with repeat miscarriages and ART fail-

ures, a strong impact of the C677T MTHFR isoform is observed. Both partners could be responsible for the failure, not only the woman. MTHFR gene mutation has been recognized for many years as being one of the possible causes of repeat first trimester fetal losses Hypercoagulability being linked to hyperhomocysteinemia, the patients are treated with anticoagulants to reduce the risk of thrombotic events in addition to 800µg of 5-MTHF. Low molecular weight heparin (LMWH) is administered starting at the beginning of the pregnancy.

ASSISTED REPRODUCTIVE FAILURES AND MTHFR

In patients with repeat losses and ART failures, a strong impact of the C677T MTHFR isoform has been observed. Oocyte donation failures are generally attributed in part to the male partner. It is imperative to address a question regarding oocyte and sperm donors, since MTHFR testing is not usually obtained in the screening of donors by banks storing and providing gametes. Also, testing should be mandatory in couples with repeat miscarriages ART failures. Testing the donor, the recipient and the male partner should be considered as proper medical practice. Couples with repeat intra uterine insemination (IUI) or in-vitro-fertilization (IVF) failures should be tested for MTHFR mutations. If MTHFR mutation is detected, the patients should be treated with 5-MTHF with vitamin complements for 2 to 4 months before any further attempts. Successful experiences with such treatments have been reported.

ABNORMAL SEMEN ANALYSIS AND MTHFR

A negative impact of MTHFR C677T isoform on semen quality has been reported and 5MTHF allows a fertility improvement. It may concern sperm morphology, oligoasthenospermia and DNA tertiary structure. The paternal effect on embryo development should not be overlooked as trophoblast growth and differentiation are strongly under paternal control and request a high methylation activity. Testing sperm donors in cryopreservation banks should also be advocated.

PREMATURE OVARIAN INSUFFICIENCY AND MTHFR

It has also been speculated that some cases of early ovarian failures could be attributed to an abnormal cellular methylation process. Testing include a serum AMH (antimullerian hormone), a pelvic ultrasound with evaluation of the ovarian volume and number of antral follicles. All patients who are affected with a prematurely low ovarian reserve should be tested for a possible MTHFR mutation.

L-5-MTHF/Folic Acid and Prevention of NTDs

It has been very well established that folic acid supplementation before conception and during pregnancy (first trimester) significantly reduces the incidences of NTDs. Documented evidence suggest that the decrease in incidences is directly proportional to the dose of folic acid and the maximum protection from NTDs is achieved at a dose of 5 mg/day. (Table 1).

Table 1: Dose-dependent reduction of NTDs with folic acid.

Dose	% prevention of NTD
400 µg	36
1 mg	57
4 mg	82
5 mg	85

The Motherisk guidelines suggest use of 5 mg/day folic acid several months before conception and until the end of first trimester. According to the guidelines, compliance is less than optimal among women using prenatal vitamins, rendering many women unprotected against NTDs. Taking a higher dose of folic acid will allow achievement of protective folate levels, even with partial compliance. Similarly, the Society of Obstetricians and Gynaecologists of Canada guidelines recommend 5 mg folic acid per day additionally with folate-supplemented diet at least 3 months before conception and continued until 10 to 12 weeks after conception. it has been concluded in many articles that L-5-MTHF-Ca is bioavailable to an extent similar or slightly higher than folate.

Also international organizations like the European Food Safety Authority, Food Standards Australia New Zealand, and Joint Food and Agriculture Organization/ World Health Organization Expert Committee on Food Additives have concluded that L-5-MTHF has a similar or slightly higher bioavailability and bioefficacy than folic acid.Thus, if the optimum dose of folic acid for maximum protection from NTDs is 5 mg and the bioavailability of folic acid and L-MTHF is similar, the optimum dose of L-MTHF is 5 mg.

CONCLUSION

The MTHFR polymorphism hampers folic acid metabolism leading to increased tHcy levels, MTHFR polymorphism may increases the risk of infertility and pregnancy complications like NTD & Spina bifida and encephalopathy etc.

In addition, all patients with repeat IVF failures or miscarriages must be tested for MTHFR isoforms. In light of the above findings, we can suspect that there will be an increase in deliveries of progenies with a high rate of congenitally inherited MTHFR isoforms.

The L-5-MTHF is the active form of folic acid whose action is independent of MTHFR enzyme. Supplementation of L-5-MTHF in women can effectively improve folate status irrespective of MTHFR polymorphism and significantly reduce pregnancy complications and can ensure better pregnancy outcomes.

Studies have shown that L-5-MTHF has similar bioavailability to folic acid. Thus, 5 mg of 5-L-MTHF appears to be a better alternative to 5 mg folic acid in preventing pregnancy-related complications associated with hyperhomocysteinemia irrespective of MTHFR polymorphism.

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Attendance	85%
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Candidate can take maximum of three attempts	
Entrance Examination Date	**1st week of December, 2021**
Entrance Examination Fee	INR 2,500/-+ 18% GST = INR 2,950/-
Syllabus for Entrance Examination	Reproductive Endocrinology, Andrology, Basic Embryology, ICMR Guidelines, Basic Genetics, Endoscopy
Course Fees	INR 3 lakhs + 18% GST = INR 3.54 lakhs (excluding accommodation and travel)
Last date for sending Applications	**15th November, 2021 for 1st January, 2022 Batch**

Time and Place of Exam will be intimated

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Dr Padmrekha Jirge
Editor: JHRS

POSITION STATEMENT FROM ISAR

RECOMMENDATIONS FOR COVID VACCINATION DURING FERTILITY TREATMENTS AND EARLY PREGNANCY

INTRODUCTION
Vaccination plays an extremely important role in achieving herd immunity against this infection. ISAR supports strict adherence to its earlier recommended COVID appropriate behaviour strategies such as masking, use of social distancing, and rigorous attention to hand washing, for disease prevention. It also supports the use of triage for both patients and hospital staff, appropriate PPE, implementation of travel restrictions and quarantines as indicated.
Patients are disappointed by the delays in treatment, additional steps such as multiple COVID-19 tests during treatment, and the inability of partner to attend the clinic with them. Motivations, perceptions, and responsible behaviours of the patients will help fertility clinics develop successful strategies to ensure safe reproductive care.
The following recommendations are developed based on the currently available and published evidence and relevant guidelines from FOGSI, FIGO, ASRM, ESHRE, British Fertility Society (BFS) and Society for Male Reproduction & Urology (SMRU).

COVID-19 VACCINES
Currently available vaccines against Covid-19 contain one of the following: mRNA, adenovirus as vector and protein subunit. Available evidence shows that vaccination is effective against symptomatic and asymptomatic infection, hospitalization, severe-critical disease, and mortality.

COVID-19 VACCINES IN INDIA
There are three different vaccines against Covid available in India. They are Covishield incorporating a replication incompetent adenovirus vector; COVAXIN, a mRNA vaccine and Sputnik -V, an adenovirus vectored vaccine. Central Drugs Standard Control Organisation (CDSCO) granted approval of restricted emergency use to Covishield and COVAXIN vaccines on 2nd January 2021. Further, permission for restricted use in emergency situations was granted for Sputnik-V vaccine by DCGI on 13th April 2021. It is important to note that none of these vaccines contain live attenuated virus. All the above vaccines require two doses to be administered. Relevant information regarding the three vaccines are included in Table 1. While they do not completely prevent COVID, their effectiveness in reducing the severity of disease and mortality are considered as important factors when creating this recommendation for administration of the vaccine to women who are pregnant or to couples attempting pregnancy.

COVID-19 VACCINATION FOR PEOPLE UNDERGOING / AWAITING FERTILITY TREATMENTS
Infertile couples are an important subgroup of population at risk of developing Covid-19 due to one or more of the following reasons:
1. Need for frequent travel to access treatment and hence increased risk of exposure
2. Largely not vaccinated at present as majority of them are under 45 years of age
3. Many have certain co-morbidities such as obesity, impaired glucose tolerance or diabetes mellitus, hypertension or autoimmune disorders. Women with PCOS constitute an important group at high risk of developing severe Covid-19.
4. Possible misconceptions, and misinformation regarding safety of vaccine in pregnancy and consequent vaccine hesitancy.
Hence there is an urgent need for recommendations pertaining to vaccination for this population, to assist in engaging and encouraging them for vaccination.

1. Impact of vaccination on fertility
The concerns that Covid vaccinations may be associated with infertility are considered to be unfounded. Current evidence from a study in women undergoing consecutive IVF cycles before and after vaccination does not show any negative impact of vaccination on ovarian stimulation, oocyte or embryological parameters, in those who commenced treatment 7-85 days following vaccination. Hence, patients undergoing fertility treatment should be encouraged to receive vaccination as soon as they become eligible for vaccination in the national programme.

2. Vaccination strategy in men and women awaiting fertility treatments

Women who are fully vaccinated may start their fertility treatment within a few days after the last dose (avoid COVID-19 vaccination at least three days prior and three days after their procedure). The treatments include any surgical procedures, oocyte retrievals, embryo transfers or intrauterine insemination. The short time interval is to allow for the immune reaction to settle in and to tide over any transient febrile reaction following vaccination. The side effects make it difficult to determine if a post-procedure fever is related to the vaccine or to a developing infection related to the procedure. Any anaesthesia administered may further affect the thermoregulation transiently.

Women who are at high risk of developing COVID-19 during the course of treatment or at a high risk of pregnancy related complications should be advised to prioritize vaccination before pregnancy.

Men who have completed vaccination may commence treatment and provide semen samples a few days after vaccination and a protracted wait is not necessary.

Those who have had any allergic reaction to the vaccine should proceed with treatment upon such advice from the physician. However, treatment should not be delayed to the couples while waiting for the availability of vaccine.

3. Time interval between vaccination and pregnancy

Most data regarding the safety of vaccines is from animal studies or women who had taken vaccination unknowingly when pregnant. Since the vaccine is not a live virus, there is no reason to delay pregnancy attempts because of vaccination administration or to defer treatment until the second dose has been administered.

4. Recent COVID-19 infection and vaccination

Currently, it is known that, antibodies may be identified for up to six months or longer, following an infection with COVID. It is recommended that a physician's opinion is sought prior to commencing any fertility treatment, in particular in those who needed hospitalization both regarding the timing of treatment and of vaccination. Nature of treatment and possible risk of thromboembolism (TE) thereof should be discussed with the physician. Vaccination may be advised 12 weeks form infection or 4-8 weeks from recovery.

5. Vaccination of pregnant women

There is emerging data that demonstrate that pregnancy is a high-risk condition for the development of severe disease and increased mortality associated with COVID-19. Though pregnant women were not included in the initial COVID-19 vaccine trials, the data of safety comes from women who received vaccination without being aware of their pregnancy. However, it is important to note that there should be a gap of 14 days before and after vaccination against covid and any other vaccine/s routinely administered during pregnancy.

COVID-19 VACCINATION AND RECOMMENDATIONS FOR REPRODUCTIVE CARE PROVIDERS

• Most of the healthcare workers including those in fertility clinics are fully vaccinated by now in India. ART centres should prioritize vaccination of any new member of staff.
• Reproductive health care provider must tailor vaccination discussions appropriately with all patients and provide accurate information or suggest reliable sources about COVID safe and appropriate behaviour and vaccination.
• Acknowledge fears, anger, and other negative emotions
• Share personal experience and vaccination confidence.
• Serve as vaccine ambassadors and help promote vaccine utilization and combat vaccine hesitancy and misinformation, to facilitate the health and safety of our patients, our communities, and overall society.

SUMMARY RECOMMENDATIONS ON VACCINATION AND FERTILITY TREATMENT

• All the available vaccines - Covishield or Covaxin Sputnik-V can be used in both men and women contemplating pregnancy.
• All patients contemplating pregnancy or are pregnant should have accesses to all available information about the safety and efficacy of the vaccines.
• In men and women who receive the vaccine, it seems prudent to postpone assisted reproduction treatments for at least a few days (ideally 3-4 days) after the completion of vaccination.
• In patients who have had COVID-19 disease and could have developed immunity, vaccination may be advised 12 weeks from infection or 4-8 weeks from recovery
• Currently available data do not report a negative impact of COVID-19 vaccination during the periconceptional period and pregnant women should also have access to vaccination
• COVID vaccine can be simultaneously administered along with other vaccines like tetanus and influenza during pregnancy, but a 14-day interval between vaccines is recommended

CONCLUSION

Infection with COVID-19 can lead to ongoing illness across a wide array of organ systems after regression of disease. Prevention strategies should continue to be of utmost importance, not only to prevent death from acute disease, but also to prevent long term complications and ailments that affect a significant percentage of individuals who contract COVID-19. Effective management of COVID-19 cases will depend on the success of vaccination campaigns and the attainment of herd immunity, the effect of variants on disease severity and spread, and the degree to which mitigation efforts are proposed and followed. The fertility clinics should monitor and compare the outcomes of assisted reproduction treatments in vaccinated versus non-vaccinated patients. This will help in providing data to assess the safety of vaccines for pregnant women and their offspring and guidance for future recommendations.

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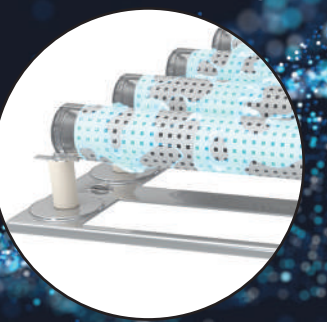

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INDEPENDENTLY TESTED AND PROVEN
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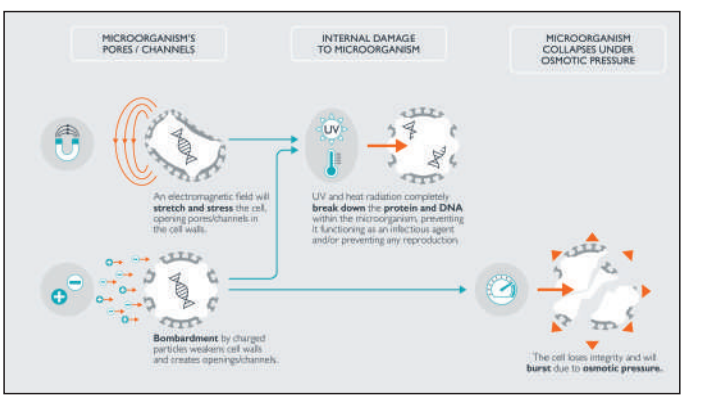

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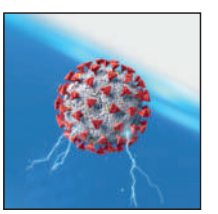
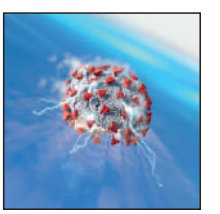
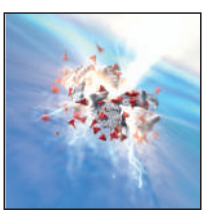
BACTERIA	• MRSA • *Bacillus subtilis* • *Staphylococcus epidermidis*	• Tuberculosis • *Escherichia coli* • *C. difficile*
MOULD SPORES	• *Aspergillus niger*	
VOCs	• *Formaldehyde*	



NanoStrike attacks the pathogen, perforating cell walls



DNA and protein within the cell are destroyed



Cell bursts due to osmotic pressure

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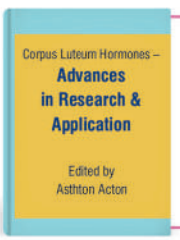
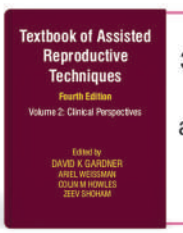
>800 Scientific Papers/Studies are available on Progesterone Capsules[9]

NMP Capsules : Approved in **>80 Countries** Worldwide, including **US, Europe, Canada & New zeland**[3,4]

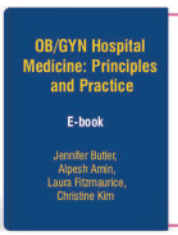
Vaginal NMP is Backed by recommendations from various International Textbooks



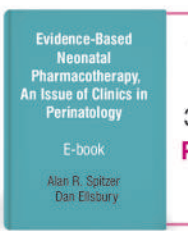
Vaginal Progesterone in women with no prior spontaneous preterm birth & cervical length of 20mm or less than 24 weeks gestation or earlier[5]



32 RCTs involving 9839 women: I.M. & **Vaginal Progesterone** are equally effective in providing **luteal phase support**[7]



Vaginal Progesterone preferentially prolongs pregnancies complicated by a **shortened cervix**[6]



100 mg **Vaginal Progesterone Suppositories OD** from 24 to 34 weeks **significantly reduces Premature delivery** from 29% to 14% as compared to placebo[8]

1. Gian Carlo Di Renzo et al.; Best Pract Res Clin Obstet Gynaecol. 2020 Nov;69:2-12. 2.Czyk A et al. Gynecol Endocrinol 2017 Jun; 33(6): 421-424 3. Press Release January 22 2016,Information : Approval has been granted for UTROGESTAN Vaginal Capsules 200mg 4. Australian Public Assessment Report for Progesterone June 2017 (AusPAR Prometrium/Utrogestan Besins Healthcare Australia Pty Ltd. PM -2014-03908-1-5 Final 1 June 2017) 5.Textbook of Corpus Luteum Hormones—Advances in Research and Application,Edited by Ashton Acton,Page no.83 6. OB/GYN Hospital Medicine: Principles and Practice E Book, Authors : Jennifer Butler, Alpesh Amin, Laura Fitzmaurice, Christine Kim, Page no.139 7.Textbook of Assisted Reproductive Techniques Fourth Edition Volume 2 : Clinical Perspectives, Edited by David. K Gardner,Ariel Weissman,Colin M. Howles,Zeev Shoham, Page no. 154 8. Evidence-Based Neonatal Pharmacotherapy, An Issue of Clinics in Perinatology, Author :Alan R. Spitzer, Dan Ellsbury, Page no.8 9. Number of Studies/Clinical Papers Reflecting Progesterone on Pubmed accessed on 29th Jan 2021 *Data on file NMP : Natural Micronized Progesterone SLDS : Softlayer Delivery System (Oral & Vaginal NMP Capsules) ART : Assisted Reproductive Technique

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Mirza F, et al. Dydrogesterone use in early pregnancy. Gynecol Endocrinol. 2016;32(2):97-106. † Schindler AE. Progestational effects of dydrogesterone in vitro, in vivo and on human endometrium. Maturitas. 2009;65(1):S3–S11.
^ 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. * As Prescribing Information of Solfe, version 1; Dated: 25th July 2013

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