THE NEWSLETTER

isar EXPRESS

Indian Society for Assisted Reproduction

ISSUE 2, 2020-2021

The Visionary & The Founder

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

Inspire confidence

Reference: 1. Data on file. IQVIA Market Data Analysis. Dec 2019; 2. Christianson MS, et al. J Assist Reprod Genet 2017;8:1059–1066; (edited)
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

For further information refer to full prescribing information or write to:
Merck Specialities Pvt Ltd., Godrej One, 8th Floor, Pirojsha Nagar, Eastern Express Highway, Vikhroli (East) Mumbai - 400079 www.merck.co.in
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MERCK

PRESIDENT'S MESSAGE

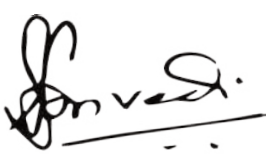
Dear Colleagues
Wish you all a very Happy New Year with new beginnings and new opportunities!

The last year had been a roller coaster ride for all of us physically, mentally as well as financially. On the brighter side it helped us realize how important our health is and we must cherish and nurture it. We have the largest vaccination program against COVID 19 going on with the aim of covering around 3 crores frontline workers and 27 crores of those who are most vulnerable to the disease by end of July 2021. This is a commendable achievement and has shown a ray of hope and optimism in coming days.

In meanwhile we are once again here with our next issue of ISAR express and we have tried to bring a holistic package of academics with practical approach. From this edition we have added a special section highlighting the glorious history of ISAR, beginning with our founder President, Dr. M. N. Parikh who's vision conceptualized ISAR. The journey of ART in India, from being a developing country to being a mecca for sub- fertile couples from all over the world has been tremendous. This edition has a variety of interesting topics which will help us in clinical decision making like Adjuvants in IVF, Freeze all, Female genital tuberculosis, Ovarian rejuvenation, Gonadotropins in IUI, Minimizing errors in IVF lab, Obesity & thyroid, Selecting best incubator, Optimizing ET results. We have also included an article on our pharma partners who have always helped us and brought the latest technologies and drugs which has helped us grow holistically.

I hope you would love reading this issue and appreciate the efforts of team ISAR 2020-21 in compiling them.

Wishing you all a good health.
Yours sincerely



Dr. Prakash Trivedi
President ISAR 2020-2021

During Pregnancy, offer Meera the XTra strength of iron to OVERCOME severe Iron Deficiency Anaemia with

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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

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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.

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

MAT-IN-SANG/LIV-21-000001

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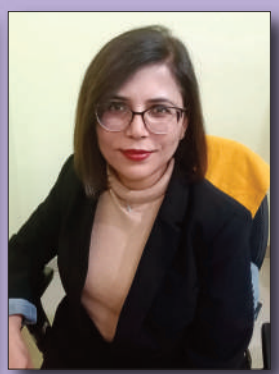
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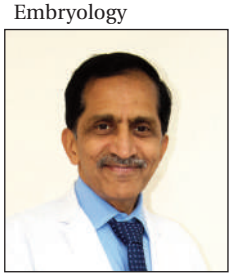

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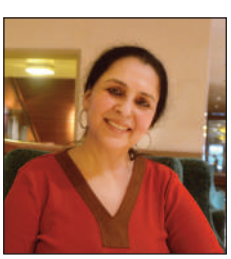

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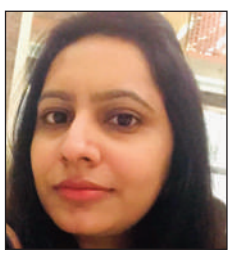

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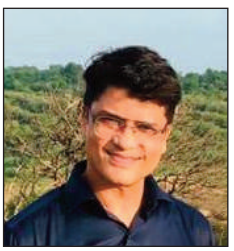

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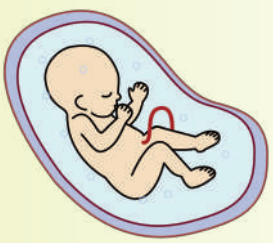
DR. Sadhana Desai

"A person's most useful asset is not a head full of knowledge, but a heart full of love, an ear ready to listen and a hand willing to help others."

DR SADHANA DESAI ENDOWMENT FUND

FINANCIAL AID FOR COUPLES UNDERGOING IVF / ICSI



ABOUT THE FUND

• Considering the increasing number of couples seeking IVF treatment and the exorbitant costs involved, Dr Sadhana Desai established this fund. Indian Society for Assisted Reproduction (ISAR) graciously agreed to be part of it.

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

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

APPLICATION PROCESS

1. Patient Application Form

a) To be downloaded from the ISAR Website at https://fertilityivffund.com/patient_application_form.php

b) To be filled by the couple and submitted to the IVF centre along with the following documents

c) Documents required:

i. PAN Card / Ration Card / Passport / any other document proving Indian Nationality

ii. Aadhar Card

iii. Marriage Certificate

iv. Last 3 years IT Returns or Bank Statements from all accounts for the last financial year

2. Clinic Registration Form - To be filled by the treating IVF Specialist and submitted online at https://fertilityivffund.com/application_form.php

3. The application is reviewed by the competent authority and approved by the panel.

4. Disbursement of Funds - Once approved, the payment will be made directly to the IVF centre

For Further Details please check https://fertilityivffund.com/our-process.php

FERRING
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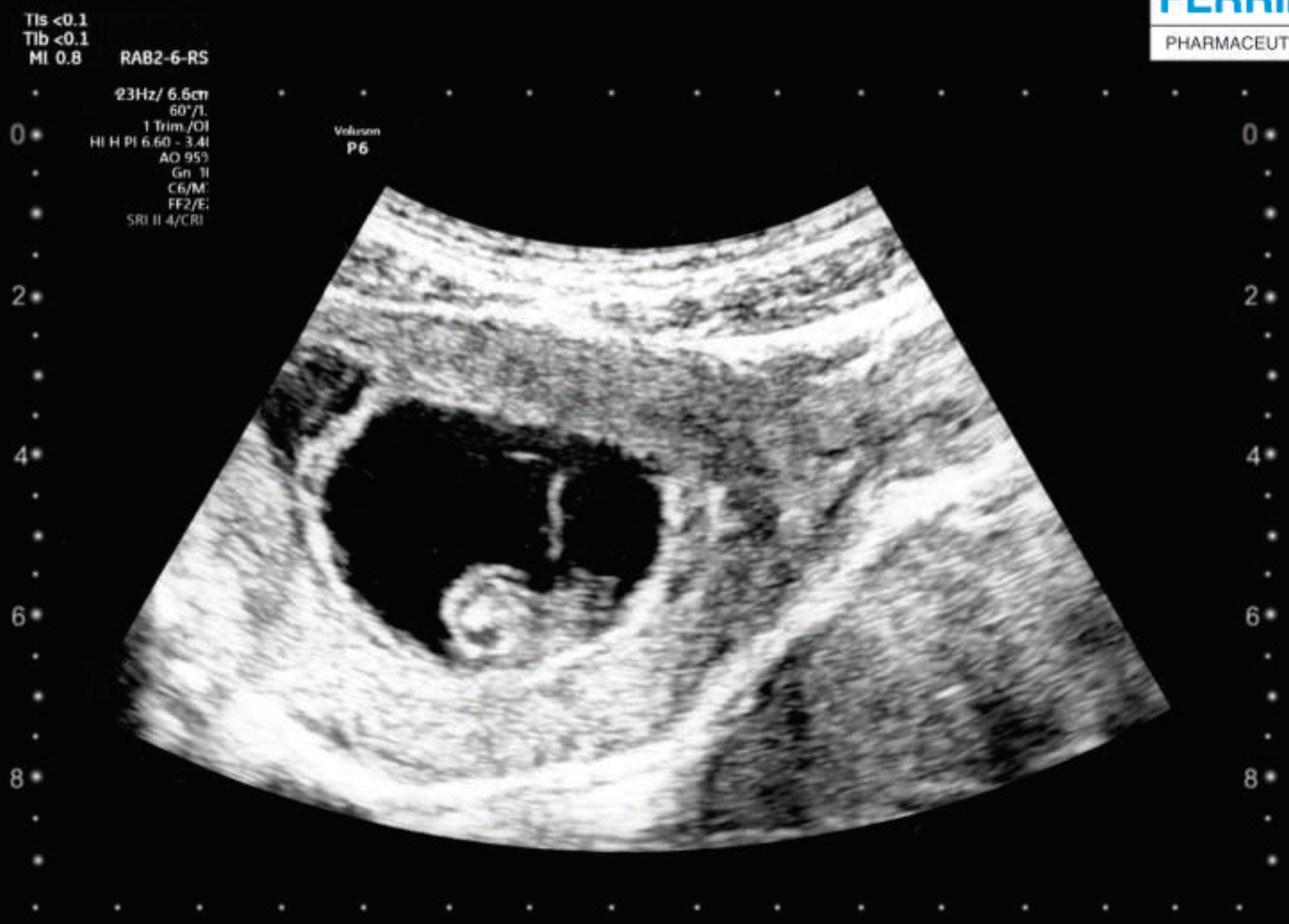

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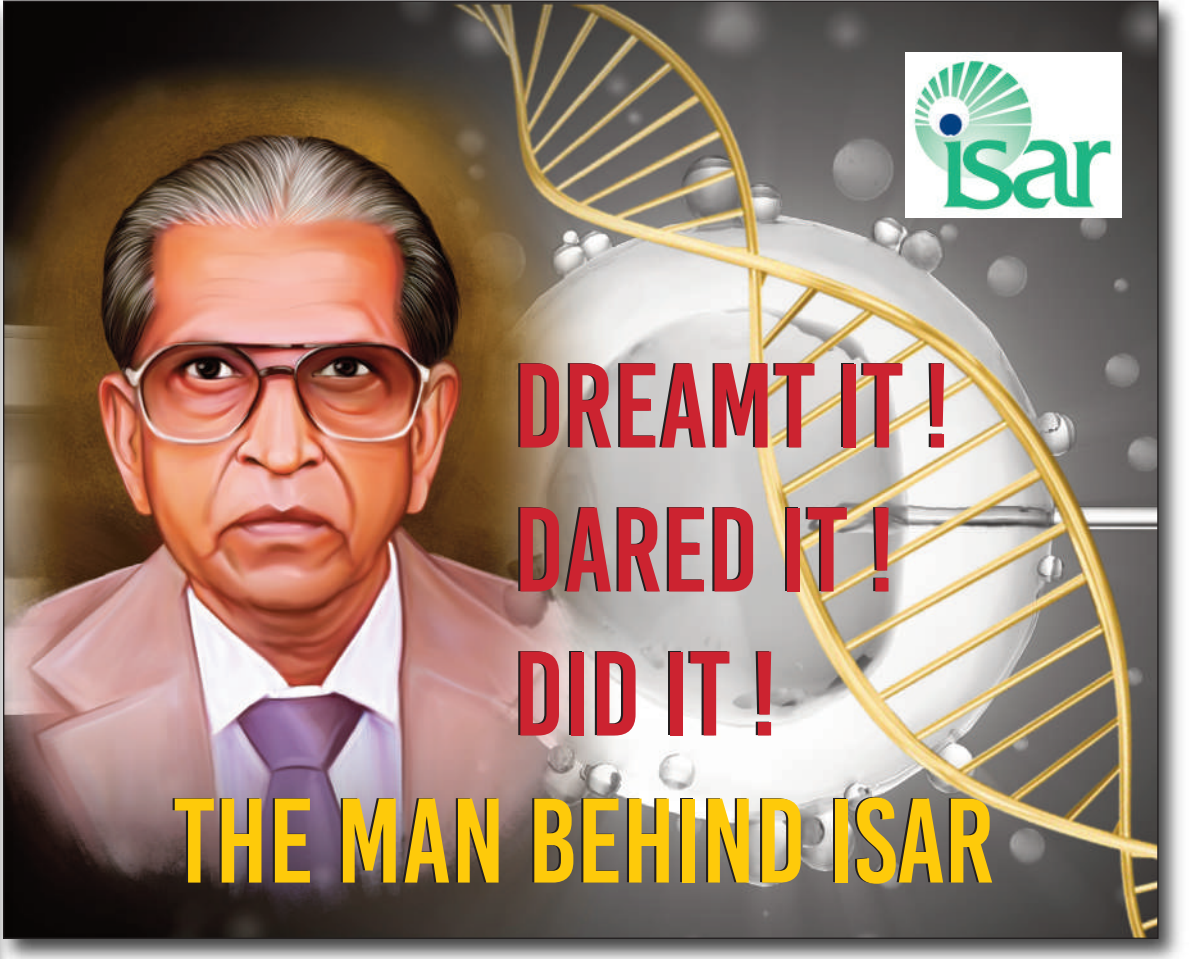

THE VISIONARY & THE FOUNDER - DR. MAHENDRA N. PARIKH

Art for the treatment of infertility is among the extraordinary accomplishments of the 20th century. India's contribution to this field was parallel to that of Bob Edwards and Patrick Steptoe. The work of Subhash Mukherjee culminated with the birth of Durga in Kolkata just three months after the world's first IVF baby Louise Browne. Since then, Indian stalwarts have dedicated themselves to this field.

In 1990 art was in the nascent phase in India with a handful of ivf clinics. A concerted effort was required to establish scientific work in the field of ivf in our country. This need was most understood by the brilliant scientific mind of none other than Dr. Mahendra N. Parikh. Our visionary founder-president Dr.M.N. Parikh called for a historic meeting of reproductive medicine specialists and gynecologists on Saturday, the 16th of February 1991, at 6.00 pm at the Apex Hall, IMA building, Mumbai. The Indian Society for Assisted Reproduction was born with a handful of founder-members. The original Logo of isar was handcrafted by Dr Parikh. Dr. Mahendra Parikh was unanimously elected to chair the meeting as proposed by Dr. M K Patel & seconded by Dr. S. N. Daftary. This meeting, after considering various aspects of the proposal unanimously decided to form the Indian Society for Assisted Reproduction and later on passed the memorandum of ISAR and headquarter of the Society shall be in greater Bombay. The main aim and objective of the society would be to bring together Medical personal allied scientists, organizations, philanthropists and institutions interested in various aspects of Assisted Reproduction for helping infertile couples and for developing newer and more efficient technologies for Family Welfare. It was also decided that society would collect, pool and distribute to the members of the society and other interested party's information and developments in the fields of Assisted Reproduction and relevant research activities concerning Family Welfare and to make assisted Reproduction easily available to needy infertile couples irrespective of caste, color, creed and social status.

Apart from these many other objectives were decided like-

a) To create public awareness and opinion in matters relating to Assisted Reproduction

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2002	2006	2012	2020
EISG[1]	MERiT[2]	MEGASET[3]	MEGASET-HR[4]
Menopur® vs rFSH alfa*	Menopur® vs rFSH alfa*	Menopur® vs rFSH beta#	Menopur® vs rFSH alfa*
Total patients 781	Total patients 731	Total patients 749	Total patients 619

Total number of patients enrolled in *Randomized Controlled Trials*[1,2,3,4] 2,880

*Gonal-F #Puregon **The primary outcome in all listed non-inferiority trials is ongoing pregnancy rate. See study references ***RCTs: Randomized Controlled Trials

EISG: The European and Israeli Study Group on Highly Purified Menotropin versus Recombinant Follicle-Stimulating Hormone MERIT: Menotropin versus Recombinant FSH in vitro Fertilisation Trial MEGASET: Menopur in GnRH Antagonist Cycles with Single Embryo Transfer
MEGASET-HR: Menopur in GnRH Antagonist Cycles with Single Embryo Transfer - High Responder

References :

1. Diedrich K et al. The European and Israeli Study Group on Highly Purified Menotropin versus Recombinant Follicle-Stimulating Hormone. Efficacy and safety of highly purified menotropin versus recombinant follicle-stimulating hormone in in vitro fertilization/intracytoplasmic sperm injection cycles: a randomized, comparative trial. Fertil Steril. 2002;78(3):520-528.
2. Andersen AN et al. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. Human Reprod. 2006;21(12):3217-3227.
3. Devroey P et al. A randomized assessor-blind trial comparing highly purified hMG and recombinant FSH in a GnRH antagonist cycle with compulsory single-blastocyst transfer. Fertil Steril. 2012;97(3):561-571.
4. Witz CA et al. Randomized, assessor-blinded trial comparing highly purified human menotropin and recombinant follicle-stimulating hormone in high responders undergoing intracytoplasmic sperm injection. Fertil Steril. 2020;114:321–30.

MENOPUR® [Menotropin for Injection IP]

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.

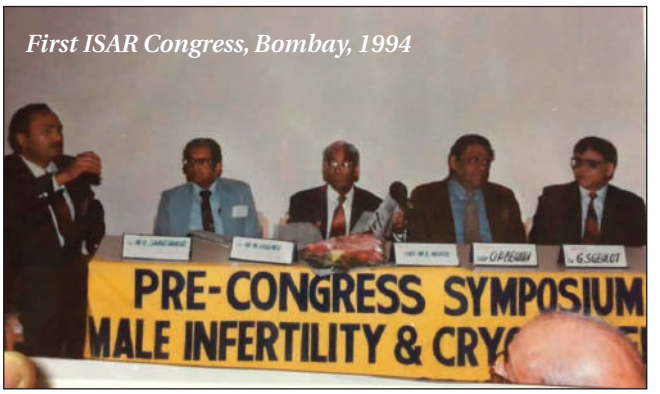
Date of Revision: 7th August 2020

FERRING PHARMACEUTICALS

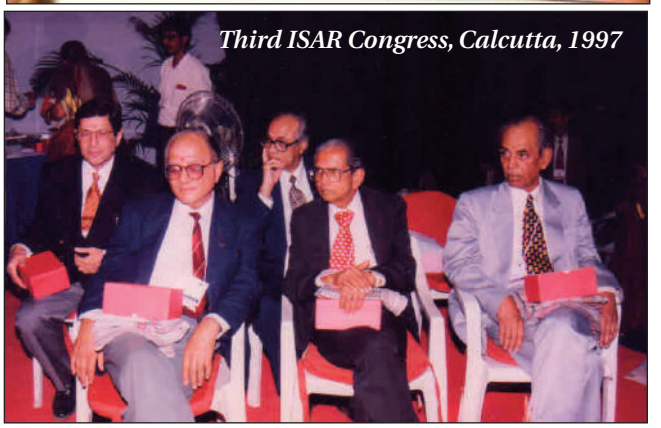
Ferring Pharmaceuticals Pvt. Ltd.
The Capital, Unit 509/510, A wing,
5th floor, Bandra Kurla Complex, Bandra(E),
Mumbai 400051, India

FPPL/C4/20/MNP/42

For the use only of registered medical practitioner or hospital or laboratory.



First ISAR Congress, Bombay, 1994

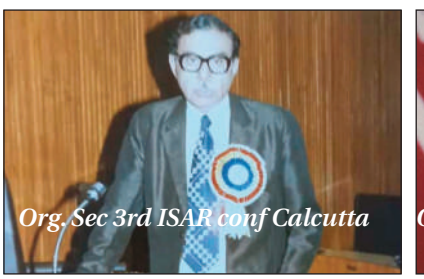

Third ISAR Congress, Calcutta, 1997


Fourth ISAR Congress, Chennai, 1998

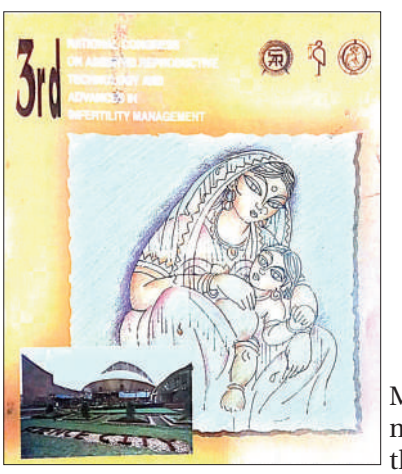
and Family Welfare.
b) To promote at all levels of society, education in all aspects of assisted Reproduction and relevant developments in the field of Family Welfare.
c) To advise and coordinate with other organizations, and Government, corporate and other authorities on technical and clinical research aspects of Assisted Reproduction and relevant developments in the field of Family Welfare.
d) To promote, sponsor and organize lectures, meetings, orations, seminars, symposia, panel discussions, workshops training programs, conference, etc. with the purpose of Page- 3 - exchanging and advancing knowledge on all aspects of Assisted Reproduction including its relevant Family Welfare aspects.
e) To promote, sponsor, assist, organize and carry out research in any aspect of Assisted Reproduction and Family Welfare.
f) To collaborate with, assist, subscribe to and affiliate with any other body – Indian, Foreign or International – having objects altogether or in part similar to those of the society.
g) To create orations, awards, fellowships, scholarships, prizes etc., for scientists interested in any aspect of Assisted Reproduction and relevant Family Welfare .
h) To promote, sponsor and publish bulletins, news letters, journals, books etc., to serve as a medium of communication and advancement of knowledge amongst the members of the society and other individuals, organizations, agencies and institutions interested in Assisted Reproduction and relevant Family Welfare .
i) To do or get done anything necessary or desirable for the promotion and fulfilment of the aims and objects of the society.
j) To receive donations in cash or kind for the various activities of the society.
The meeting thereafter, unanimously elected the following Executive Committee to hold office for 7 years.
1) Dr. Mahendra Parikh , President
2) Dr. C. L . Jhaveri, Hon. Patron
3) Dr. Mehroo Hansotia, Senior Vice President
4) Dr. Firuza Parikh, Second Vice President
5) Dr . M. K Patel , Hon. Secretary General
6) Dr. Narendra Joshi, Hon . Jt Secretary
7) Dr. Sharad Gogate, Hon. Treasurer
8) Dr. Jayashree M Patel, Hon. Jt Treasurer
9) Miss Nivedita Tank, Hon. Clinical Secretary
10) Dr. Murari Nanavati, Hon . Librarian
11) Dr. Shirish N Daftary
12) Dr. Shyam V Desai
13) Dr. Vinod B Joshi
14) Dr. Rohinee Merchant
15) Dr. Veerbala Parikh
16) Dr. Kuntal Rao
17) Dr. Kamla Selvaraj
18) Dr. D K Tank
Subsequently the following were co-opted by the Executive Committee on 6/8/1991:
Dr . B . N . Chakravarty, Dr. R. P. Soonawala, Dr . Mohanlal Swarankar,. Dr. C. L Jhaveri was unanimously elected as Hon. Patron of the Society.
This meeting was instrumental in making the constitution and various other documents which laid a solid foundation of our society till date.
From its inception till 7/6/2000 the office of the Society was located at 43, Vasant, Off Carter Road, Khar, Mumbai - 400052 , the premises provided by Dr. Mahendra Parikh for use free of cost. On 7/6/2000, the society purchased it's own office premises at 23A, 2nd floor, Elco Arcade, 84 , Hill Road, Bandra (West), Mumbai – 400050. Dr.


Org. Sec 1st ISAR conf Mumbai


Org. Sec 2nd ISAR conf Jaipur


Org. Sec 3rd ISAR conf Calcutta


Org. Sec 4th ISAR conf Chennai




Org. Sec 5th ISAR conf Ahmedabad

M.N.Parikh remained president till the year 2000.

The following National Congresses were held while Dr. M.N. Parikh headed ISAR:

Bombay- November 1994: the theme was ovulation induction and male infertility & IUI & IVF.

Jaipur- February 1996: the theme was male infertility & cryopreservation, IVF, Endoscopic surgeries and microsurgical recanalization in infertility. Dr. M. L. Sawarankar

Calcutta- February 1997: Theme- andrology IVF, organizing chairperson was none other than Dr. B.N.Chakravarty

Chennai- February 1998: Theme- endoscopy & IVF, Dr. Kamla Selvaraj

Ahmedabad- February 1999: Theme- operative endoscopy & cryopreservation, Dr. Manish Banker.

This article is dedicated by Team ISAR-2020-21 to our Founder President, Dr.M.N. Parikh and to the journey of ISAR. We have talked to key attendees of the first meeting, Dr. Parikh's family, friends and colleagues to understand the vision of the stalwart behind our organization.

MAHENDRA N. PARIKH

M.D., D.A., FICOG, FICS, FIMSA, FICMCH

Dr. M.N. Parikh was born on the 16th of December, 1927 in Pethapur a small town near Gandhinagar, Gujarat. He spent most of his childhood in Sangli, Maharashtra as his father conducted his business from there. Dr. Parikh is the eldest among seven siblings. Their parents firmly believed in gender equality. Dr. Parikh's three sisters were encouraged to study medicine and each of them shone in their chosen specialties of gynaecology, anaesthesia and pathology. His three brothers became engineers and set up their own firms in India and the USA.

Dr. Parikh was a brilliant student, topping all exams throughout his education. He excelled at Math, Chess and Table Tennis. While he was the first in the family to study medicine, over 35 others from the family have followed in his footsteps covering diverse specialisations across three continents.

While doing his residency in Obstetrics and Gynaecology, he met his wife, Shobha who played a pivotal role in his career. He rose rapidly in academics and was a professor at the JJ Hospital, the KEM Hospital and at the Nowrosjee Wadia Maternity Hospital. Meanwhile his wife, Shobha became a pioneer in the Crèche movement in India by setting up one for Pfizer. It became an iconic model across the world. At her insistence he hesitatingly started private practice.

Gradually, his practice built up and covered all sections of society. There were many patients whose lives he had saved during childbirth and they remained his diehard fans. He continued his interest in teaching and academics and his brilliance shone through when at a young age, he coauthored a Textbook of Obstetrics with his mentor Dr K. M. Masani. This was the bible for final year medical

Celebrating Dr MN Parikh's 85th birthday

students.
His passion for teaching resulted in overflowing auditoriums at the KEM and Wadia Hospitals with undergraduate and postgraduate students coming from all across Mumbai to listen to him in rapt attention. He was an astute clinician and teacher par excellence throughout his career.
In the early 1970s, he was invited to train in laparoscopy by the legendary gynaecologist, Professor John Rock, at the Johns Hopkins Hospital in Baltimore, USA.
He trained hundreds of gynecologists in this field establishing it as a specialty in India. He also spearheaded many laparoscopic camps. Dr. Parikh's team would be seen doing laparoscopic tubal sterilization in the remotest corners of the country.
A pioneer in Gynecology, Obstetrics, Laparoscopy and an author on diverse subjects as Research Methodology, he mastered the skill of conducting difficult deliveries, specially mid-cavity forceps delivery and complex laparoscopic surgeries. His helpful nature enabled him to reach out to to doctors facing difficult surgeries and obstetric procedures. He was a master trainer and those who trained under him are now master trainers themselves.
Dr. Parikh realized that our medical education was strong in its clinical aspects but lacked innovation in research. His efforts resulted in two brilliant books on research methodology, 'The ABC of Research Methodology' and 'Applied Biostatistics'.
Apart from being Founder-President of ISAR, Dr. M. N. Parikh has headed and presided over almost all the prestigious Indian associations related to Obstetrics and Gynecology such as FOGSI, MOGS, IAGE, the Nnational Association of Voluntary Sterilization, the Indian Association of Juvenile & Aadolescente Gynecology and Obstetrics. He founded and was the Chairman of the Indian College of Obstetrics & Gynaecology. The Indian Medical Association (IMA) and the Govt. of Maharashtra have awarded him and given him many accolades for his pioneering work. An avid reader and writer, Dr. M.N.Parikh has written and contributed to various research topics in reputed national and international journals.

DR. M.N. PARIKH AS A BROTHER
Dr. Virbala Parikh
(Renowned Obstetrician & Gynaecologist)

It gives me great pleasure to write about my eldest brother, Dr. Mahendra Parikh. His selfless nature and professional achievements speak of his amazing qualities and academic and professional excellence. Even though he has retired, he is always remembered and quoted in academic fields. This speaks volumes for his work and contributions.
For me, he has been next to my parents. Whatever I am today is solely because of his help and guidance. He has been like a best friend and philosopher to me. He has a positive outlook to life and he doesn't use the word "No" in his dictionary. He is always cool headed and has a knack to get his point across with anybody. May Lord Almighty, bestow him a long and healthy life.

DR. M. N. PARIKH AS A FATHER-IN-LAW.
Dr. Firuza R. Parikh
(Renowned ART Specialist)

I first met my father-in-law three months into joining the Seth G. S. Medical College. As I entered their living room I

was met by a stern-looking man who I was told performed the most complex laparoscopic surgeries and forceps deliveries and was called by many when faced with complicated surgeries. I was relieved to find him chatty, as he soon regaled me with stories of his Parsi friends. We struck a friendship that has bloomed manifold over the years.

What can I say of a man who has been a mentor, teacher, friend, philosopher, guide and a leader not just to me but to thousands?

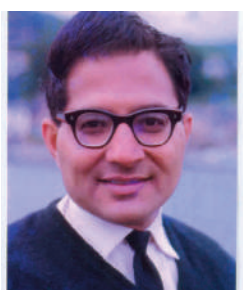
MNP as Dad was fondly called, even taught me how to make shrikhand before he taught me how to conduct a breech delivery! Few years into our marriage, I secured a Fellowship in Reproductive Endocrinology and IVF at Yale with Dr. Alan DeCherney, Dad was more excited than I and flew to meet us. He attended Grand Rounds at Yale and gave an academic discourse to the faculty much to everyone's delight. Dad made two more trips to the US while we were there. He would spend much of his time visiting my department and reading, surrounded by books in the magnificent library.

His health deteriorated after a stroke during a lecture to a packed hall at the age of 82. He struggled with his words, completed the talk, told the organisers that he had a right cerebral stroke and requested them to move him to a nearby ICU.

We recently celebrated his 93rd birthday and he gave a gracious thank you speech. We are grateful to God that we can spend time with him and thank all his friends for the constant love they shower on him

DR. M.N. PARIKH AS A FRIEND
Dr. Rohit V. Bhat
(Renowned Obstetrician & Gynaecologist)

I have a long association with Mahendrabhai for over 60



years. Working as residents at the Nowrosjee Wadia Maternity Hospital, we used to live in the family quarters of the hospital and have a nice time after duty hours. Shobhaben and children were very loveable. We used to exchange academic materials and have long discussions on problems in Obstetrics and Gynaecology.

In 1960, after completing our residency, I went to Gujarat and took up the position of Professor in Ob/Gyn while Mahendrabhai continued his academic activities at the Wadia Hospital. We kept in touch and took every opportunity to travel together for national and international conferences. I have happy memories of our travels to Berlin, Sri Lanka and the Andaman Islands. People seeing us always moving together in various conferences started calling us twin brothers. I consider Mahendrabhai as my elder brother and we have great respect for each other.

He would remain calm and collected while being late for a journey, much to the chagrin of his colleagues. I remember when we were to travel to Berlin for the FIGO conference, our flight was to take off at 03-00 hours. However he was still packing his bag till midnight! I was getting restless and he said, "the flight will not leave without us". Once he was travelling in a taxi on his way to a conference. He forgot his box of slides in the taxi. He had to use the slides for his talk in the next few hours. He was unruffled and remained calm and gave his presentation without slides. He had a very sharp recall.

I find Mahendrabhai to be a very devoted and hardworking person. He would prefer to go to the heart of any problem before deciding the course of action. He always encouraged young research workers to write their names as first authors before his name on research publications. This speaks of his determination to encourage young and upcoming doctors.

Apart from his clinical excellence, his other skill was in wielding the surgical knife. In spite of his fame, he remained a very simple man with a simple lifestyle. He has always been easily approachable to all. He would listen patiently to everyone's problems and encourage people with solutions. He always had phenomenal patience. Mahendrabhai has become a legend in his life time. Very few people achieve this kind of recognition. I miss Mahendrabhai's company. I wish him speedy recovery so that once again, we can travel together.

DR. M.N. PARIKH AS A FRIEND
Dr. Borkataky Hari Narayan
(Renowned Obstetrician & Gynaecologist)

I met this illustrious person in an AICOG congress and since then, I always accompanied him to all meetings

that I attended. My visits to Mumbai were always memorable. Whatever time I reached Mumbai, he was waiting for me with dinner laid out on the table. Often my flight reached at midnight and with the thought of not disturbing him, I would book a hotel room and ring him up from Bombay airport after arrival, so that I could

meet him next morning. But no matter what, he would call me and I had to follow! When I reached his home, I would find him sitting, ready to serve me a hot and delicious meal.
Once I organized a Scientific Session in Pinewood Residential School and I invited Dr. Parikh. His oratory prowess was appreciated by everyone. He is a father, a friend, a philosopher and a guide for me. I wish him to always be near me in spirit. Memories of our times together makes me happy. God bless him.

DR. M. N. PARIKH AS A TEACHER AND A MENTOR
Dr. Nozer Sheriar
(Renowned Obstetrician & Gynaecologist)
Dr.M.N. Parikh had a very sharp intellect and would look at the minutest detail and share a very different perspective and point of view on any topic. He was a surgeon par excellence and was a visionary, ahead of his time in his thought processes.

He had tremendous respect for the colleagues and office bearers of organizations that he headed and would always be ready to listen attentively to their suggestions regarding the wellbeing of the institution. While President of FOGSI, he significantly cut down the cost of publishing its journal with many innovative processes without compromising the quality. Even through his ill health he has always been very aware of and connected with his work. As Chairman of the Board of Trustees, he has attended all meetings and appreciated the good work done by the board. During his extraordinary and meaningful career, he has headed almost all the Indian academic organizations and has been the Founder of many. While creating ISAR as an independent organization he was questioned by his peers and colleagues as to the need for one more organization in academics. He reflected on the question and answered with his extraordinary focused vision that as the field of ART expanded, we would need a separate organization dedicated to ART and Infertility. ISAR was launched by him and as President he organized the first of its kind infertility conference in India. It served as an important platform for national and international professionals from this specialty to interact.
A joint decision was taken by his friends and colleagues to name this conference as "ART & Advances in Infertility". Along with Dr. Shyam Desai, I had the privilege of becoming the Organizing secretary of this landmark conference.

MEMBERS OF THE FIRST MANAGING COMMITTEE OF ISAR


Dr MN Parikh
President


Dr Mahendra Patel
Secretary


Dr Sharad Gogat
Treasurer


Dr Mehroo Hansotia
Sr Vice President


Dr Firuza Parikh
Second Vice President


Dr. C.L. Jhaveri


Dr. D. K. Tank


Dr. Shirish N Daftary


Dr. Murari Nanavati


Dr. Shyam V Desai


Dr. R. P. Sonawala


Dr. B. N. Chakravarty


Dr. Swarankar


Dr. Virbala Parikh


Dr. Nivedita Paghdiwala

IF THE EMBRYO CAN IMPLANT IN THE FALLOPIAN TUBE, THEN WHY NOT IN THIN ENDOMETRIAL LINING?

Dr. Seema Pandey

Dr. Rana Choudhary

Dr. Priyanka Vora

We invite feedback and comments of the readers regarding their thoughts that this article may have generated. Please email your feedback to the authors on *isar.elibrary@gmail.com*

Human implantation

Complex process requiring synchrony between embryo and receptive endometrium.

Optimum endometrial thickness?

On the day of trigger in fresh IVF cycles - 7.5mm

On the day of starting progesterone in frozen–thaw embryo transfer cycles – 7.5mm

Pathophysiology of thin Endometrium

Damage to basal endometrium or due to altered in vivo regulation and dynamic variation in biophysical parameters including pO2, pH and temperature.

Causes of thin endometrium

- Resistance to circulating estrogens
  - 1. Clomiphene Citrate (antiestrogenic)
    2. Prolonged OC Pills
    3. Chronic long standing illnesses like Diabetes mellitus and Hypertension
  - **WHAT NEXT**
  - 1. Estrogen (Step up manner) - vasodilatory effects on the uterine artery.
    2. Sr estradiol blood levels, repeat after 4 days
    3. Endometrial volume assessment
- Reduced Blood flow to the Endometrium
  - 1. ↓growth of glandular epithelium
    2. ↓VEGF expression
    3. Colour Doppler
    - Uterine Artery (PSV < 10 cm/sec, RI > 0.5 cm/sec). Mean PI uterine artery is >3
    - ↑ radial artery Resistance Index (RA-RI)
    - ↓ spiral artery blood flow activity
  - **WHAT NEXT**
  - • Vasodilators / Blood thinners?
    • Sildenafil citrate ?
    • Aspirin ?
    • Heparin ?
    • L- arginine?
- Damage to Endometrial Lining
  - • Tuberculosis
    • Previous D & C
    • PID
  - Diagnostic / Operative Hysteroscopy
- Unknown
  - Due to in vivo regulation & dynamic variation in bio-physical parameters including pO2, pH
  - **WHAT NEXT**

Factors influencing the amplitude of change in pO2 include
- Hormones
- Sympathetic and parasympathetic tone
- Myometrial and vascular smooth muscle integrity
- Arteriolar vasodilation and constriction
- Infection and Inflammation (Endometritis)

Factors affecting Implantation Due to changes at the Endometrial Interface

- Normal Endometrial thickness
- Good capillary circulation
- Low pO2
- High pH

- Thin Endometrial thickness
- Poor capillary circulation due to unbranched vessels
- High pO2
- Low pH

Potentiates

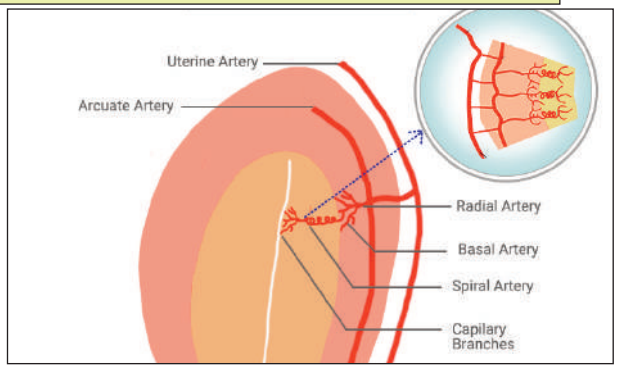
Inhibits

IMPLANTATION

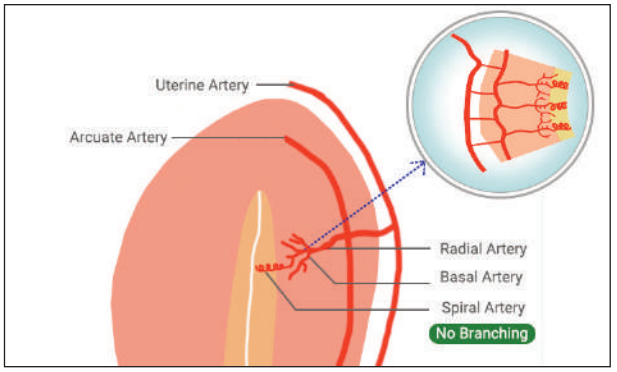
What does the literature/ research tell us?
1. Culturing embryos under optimum (low) oxygen concentrations (~5%) improves live birth rates (odds ratio (OR) 1.39; P = 0.005) as it more closely resemble natural conditions (2% to 8%) Cochrane 2012.
2. pH in female reproductive tract is graduated, with lowest pH in vagina (~pH 4.42) increasing toward Fallopian tubes (~pH 7.94), reflecting variation in site-specific microbiome and acid–base buffering at cellular level.
3. In vitro, biologic pH buffers introduced into embryo culture media helps stabilize pH and minimize deleterious intracellular changes arising from its fluctuations.

Ectopic pregnancy?
Probably Fallopian tubes & Ovaries have thin surface mucosa with good capillary distribution, hence lesser pO_2
Leading to implantation in ectopic locations ?

Normal Endometrium



Thin Endometrium



Why doesn't implantation occur in thin endometrium?

Estrogen receptor abnormalities
For the uterine lining to grow, estrogen has to bind with estrogen receptors. If these receptors are abnormal, the lining will not grow.

Oxygen tension theory

Functional layer of endometrium has plenty of small blood vessels (capillaries), in contrast to larger spiral arteries in basal layer.

With ovulation, there is constriction of spiral arteries with reduced blood flow to functional layer.

This results in reduced oxygen tension, which is good for embryo implantation.

If endometrial thickness is <7 mm, it is the functional layer that is thin, & implanting embryo would be much closer to spiral arteries, **higher vascularity & oxygen concentrations.**

High oxygen concentrations near endometrial interface layer could be detrimental compared with usual low oxygen tension of surface endometrium.

FOOD FOR THOUGHT
- What prevents implantation in thin endometrium, as against pregnancies implanting in thin fallopian tubes/ ectopic pregnancy?
- is giving very high estrogen supplementation helping or giving prolonged low dose would be beneficial ?
- Does bombarding with endometrial blood flow improving agents like arginine, low dose aspirin, Vitamin E, Pentoxifylline, sildenafil improve implantation rates?
- Is the low PO_2 (oxygen tension) in the endometrial region an important aspect that we are missing? If yes, what next …needs further research?

CLINICAL ADJUVANTS IN IVF

A BOON OR SIMPLY FUTILE?

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INTRODUCTION:
With an accelerating rate of adjuncts added to the list of clinical practice in IVF, the usage of these add-ons has befolded a dilemma for all the fertility specialists. Nevertheless, we all take the help of these adjuvants in order to overcome various barriers to a successful pregnancy. We assume that adjuvant therapies help to amplify the results of the primary IVF cycle. Right from the pre-treatment before the cycle to a good ovarian response in the cycle followed by a favorable environment for successful implantation, we have adjuvants to be used at every stage. Due to the unavailability of definitive robust evidence for most of the add-ons, large randomised controlled trials are the need of the hour. The desperation for a positive result makes both the patients and the clinicians vulnerable to explore the use of adjuvant therapies, dspite meagre evidence to support it.

ETHICS AND REGULATION OF USING THESE ADD-ONS:
Each time a cycle fails, the patient is set back both financially and emotionally. The clinicians are faced with sheer disappointment too. Hence, we are always on the lookout for any such add-on, which can probably act as that "magic element" to help achieve a pregnancy. These add- ons are non-essential services, offered to the patients in the hope of a successful pregnancy. From the point of view of ethics, the question arises if it is acceptable to offer treatment whose effectiveness has not yet been established? In the U.K, the HFEA has some power to regulate the use of add-ons in IVF with the help of the 'traffic light' method. The adjuvants are designated different colours according to the available evidence. For example, green means there is high quality evidence to support the use of an adjuvant. Red means there is no evidence to show that the adjuvant is effective and safe, and amber refers to conflicting or minimal evidence, but not supported for routine use. Since there is no such regulatory body in India, self-regulation on our part is just fair to our patients. Also, encouraging patients to ask questions about adjuvants can help them make informed decisions!

COMMONLY USED ADJUVANTS:
The aim of this article is to describe some of the commonly used adjuvants and describe their efficacy and safety in clinical practice.
1) Antioxidants: Most readily available adjuvant. Antioxidants help prevent oxidative insult to the cell membrane of oocytes. Oxidative stress is a known cause of poor egg quality, usually seen in ageing oocytes. Various antioxidants include Co-enyme Q10, inositols, vitamins, L-arginine and omega3. A recent 2017 Cochrane meta-analysis using the above antioxidants failed to show any evidence of increased LBR or CPR compared with placebo.
Studies showing the effectiveness of CoQ10 have established its action on the oocyte mitochondrial function and the meiotic spindle. It helps in the scavenging of free radicals. Presence of Q10 in the follicular fluid microenvironment is associated with superior grade embryos.Vitamins like E, A, B-complex and Vitamin D have been associated with improvement in the oocyte- endometrium quality and in cases of recurrent pregnancy loss. Omega3 is known to stimulate prostaglandin synthesis and steroidogenesis, thus improving the cell-membrane composition of oocytes. A recent 2017 metaanalysis has favored the use of myoinositols for ovulation induction, especially in PCOS women. Besides acting as an insulin sensitiser and abating the effects of hyperandrogenism, it also helps in better FSH signalling and maturation of oocytes.
2) Glucocorticoids: Steroids have been known to have immune-regulatory benefits. They alter natural killer cell and cytokine activity. Cochrane data (2017) reviewed the evidence of addition of a glucocorticoid in the stimulation cycle versus a standard protocol. Whilst glucocorticoids possibly increase the CPR, there is still no conclusive evidence regarding it. But it is known to have no impact on the LBR and miscarriage rate. However, some studies have also questioned the theory that steroids could interfere with normal immune activation in early pregnancy and placental development. While patients with specific clinical histories or presence of antibodies may benefit from the immune regulatory function of steroids, the rationale for making this a standard protocol for all patients is doubtful.
3) Androgens: Poor ovarian response constitutes 9-26% of all IVF cycles. Till now, no single effective ap-

proach has been discovered to tackle the issue of POR. Androgens are available in the form of DHEA and testosterone gel. They act via increasing the intraovarian androgen concentration via Insulin growth factor-1 (IGF-1) and thus promoting follicular growth. They also aid upregulation of FSH receptors in small antral follicles and avoid granulosa cell atresia.

DHEA- In most studies, DHEA administration (75mg dose) is started 3 months prior to commencing the treatment cycle. The ideal dose is yet to be established. A recent meta-analysis showed that DHEA also acts as a metabolic precursor for steroid production, thus helping follicular growth and increasing CPR.

Testosterone gel - Testosterone gel (12.5mg%) is used for priming in the pre-treatment cycle for a period of 15-20 days. Currently, the ongoing T-TRANSPORT study advocates the use of the testosterone gel 2 months prior to the start of a long agonist protocol for poor responders. This study exploites the fact that the 2 month pre-treatment may equip the preantral follicles with increased FSH receptors and hence increase the cohort of follicles surviving to the recruitable antral stage. In the most recent 2020 meta-analysis of adjuvants for poor responders, both DHEA and testosterone gel have shown beneficial effects.

4) Aspirin: Aspirin has anti-platelet and anti-inflammatory properties, thus creating a favorable atmosphere for embryo implantation. According to Cochrane database (2016) including 13 RCT'S, no evidence has been found to support the routine use of aspirin in general IVF population to increase LBR or decrease miscarriage rate. Studies suggest its use in cases of thin endometrium, where it is postulated to increase the endometrial blood flow. A recent 2017 meta-analysis showed that a daily dose of 100mg/day improved pregnancy rates in patients undergoing IVF/ICSI by its effects on implantation rates.

5) Heparin: Heparin exerts its anti-thrombotic effects by inhibition of factor Xa and thrombin. In patients with recurrent implantation failure (RIF) or in women with anti-phospholipid and anti-cardiolipin antibodies, unsuccessful pregnancy outcomes are observed due to thrombotic tendencies. Emerging evidence also shows that Heparin plays a role in endometrial receptivity by influencing trophoblastic activity and decidualisation. Three systematic reviews including a Cochrane review justify the use of heparin in women with >3 episodes of RIF. Its use should be weighed against its side-effects and cost-effectiveness. A recent 2019 meta-analysis of 935 patients observed that there are no benefits of heparin for use in non-thrombophilic women. Hence, more multicentric trials are needed to confirm its benefit.

6) Growth hormone (GH): Commonly used adjunct since 25 years in IVF, yet its role is still debated today. GH modulates the action of FSH on the ovary via IGF-1, thus facilitating follicular development. Evidence shows that higher follicular fluid concentrations of GH have been associated with better pregnancy rates. A recent review article (2019) concerning poor responders demonstrated that though GH leads to a greater number of oocytes and decreased gonadotropin dosage, there is no evidence to show an increased LBR. This also includes the most recent LIGHT trial which included women who showed an hypo-response in the previous IVF cycle. This study showed similar results, however it was stopped prematurely as the planned participant numbers were not reached. Another recent review article (2020) examines the use of GH for enhancing endometrial receptivity via its action on various molecular biomarkers. Whether the role of GH is beneficial for poor responders or poor ovarian reserve patients, or in the treatment of thin endometrium of RIF; is still under further investigation.

7) Platelet-rich plasma (PRP): PRP contains high concentration of growth factors and platelets which cite an immune response during embryo implantation. A recent 2018 RCT included 83 women who underwent PRP infusion for endometrium thickness <7mm. No statistically significant differences were found. In contrast to this, a 2017 study used PRP for 42 cycles in women with thin endometrium who underwent a blast transfer. They recorded improved embryo implantation rates with PRP. The role of PRP in patients with RIF has shown significantly higher CPR, thus reinforcing its benefit on endometrial tissue repair and receptivity. Currently, PRP is still used experimentally in IVF, as its use is not approved by the FDA.

8) Endometrial scratching: Acts by inducing inflammation of the endometrium and thus stimulating the immune pathway and promoting implantation. First proposed by Barash et al. in the year 2000, endometrial scratching has been widely used since then with varied results. Recent meta-analysis of 14 RCT's demonstrated inconclusive and contradictory results with respect to CPR,LBR or miscarriage rates due to statistical heterogeneity. Since it is a simple, quick and harmless procedure, the question arises if we should still continue doing it, considering its positive effect on the endometrium.

9) G-CSF: Affects embryo implantation via various mechanisms including trophoblastic proliferation, embryo adhesion and immune tolerance in pregnancy. Two meta-analysis (2017) by Xie Y and Kamath S showed increased CPR with G-CSF as compared to no intervention, but with low quality evidence. It plays a role in ovulation and LUF syndromes by increasing the neutrophil content in the thecal layer of oocytes, thus promoting successful ovulation. It has also been used for poor responders and in cases of thin endometrium in both fresh and frozen cycles. A 2016 RCT by Aleyasin et al. used G-CSF for patients with repeated IVF failure (300ug S.C 1hr before embryo transfer) and found promising results! Due to inconsistent studies, the use of G-CSF is still considered off-label.

10) Vasodilators: Vasodilators like sildenafil cause uterine smooth muscle relaxation and help increase the blood flow. This has a beneficial effect on the endometrial thick-

ness and receptivity. A cochrane review (2018) consisting of 15 trials showed increased chances of pregnancy with the use of sildenafil. Additionally, the use of vasodilators was associated with certain side effects like tachycardia and headache. More conclusive studies are needed to determine when to use and how much to use.

CONCLUSION:

In the pursuit to maximise success rates, the use of various add-ons in an IVF cycle has become inevitable today. Most of these add-ons have a reasonable pathophysiological basis, but the ideal evidence is still lacking. Although some of the add-ons discussed may have a bright future, more well designed and randomized studies are needed to justify evidence-based practice. Keeping this in mind, clinicians should keep the patients well-informed and help them understand the benefit-risk ratio of using any adjuvant. After –all, the use of these add-ons adds to the financial burden of the already harrowed couple. Below is a summarised table of all the above discussed adjuvants. Thus, using an adjuvant wisely, after taking all the factors into consideration can prove to be in the best interest of the patient!

ADJUVANTS	*ADMINISTRATION*	*EVIDENCE*
Antioxidants	Pre-treatment & Stimulation cycle	No statistically significant data for routine use.
Glucocorticoids	Peri-implantation period	No statistically significant data for routine use.
Androgens	Pre-treatment	More studies needed for use in patients with auto-antibodies. Conflicting results. Larger RCT's and further research needed.
Aspirin	Stimulation cycle & Post-embryo transfer	No statistically significant data for routine use.
Heparin	Post-embryo transfer	No statistically significant for routine use. Beneficial for patients with thrombophilia.
GH	Stimulation cycle	Inconsistent, conflicting results. Further research needed.
PRP	Stimulation cycle	Experimental use. No meta-analysis available yet.
Endometrial scratching	Pre-treatment	Inconclusive, contradictory results. Larger trials needed.
G-CSF	Stimulation cycle	No statistically significant data for routine use.
Vasodilators	Stimulation cycle	Minimal evidence to support its use.

"FREEZE-ALL" … FOR ALL?

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The successful cryopreservation of human embryos was first reported in 1983 using slow-cooling technique and in 1984, Zoe, a child born after transferring the frozen embryo was reported. This amazing event changed the course of an IVF treatment and led to the development of many new concepts. Eventually, the method of rapid-cooling and thawing known as vitrification was invented which bypassed the difficulties and drawbacks associated with slow-cooling. After the delivery of a child using this technique in 1990, it started to gain a lot of popularity. Now, the times have changed and after 20 years of the birth of that child, we are stuck with a different dilemma – whether to freeze all embryos? Or do we still do a fresh embryo transfer? Given the high success rate of this technique because of the improvement in the laboratory conditions and the ease it provides to doctor and the patient, it is very tempting to move towards the policy of freeze-all for all. But are we there yet? Let us go through what all happened.

THE TRIGGERING FACTOR

The first randomized study published by P. Humaidan *et al.* in 2005 showed us that we could use a GnRH agonist for triggering of final oocyte maturation in an antagonist cycle. But then it was seen, as also reported by G. Griesinger *et al.*, that with the use of GnRH agonist trigger and doing a fresh embryo transfer, the likelihood of pregnancy was drastically reduced. On the other hand, the possibility of developing an OHSS was almost completely eliminated by using this trigger. Many articles started to show up regarding the use of this trigger, but the challenge was to rescue the luteal phase as the agonist trigger caused leuteolysis and made it almost impossible for the implanted embryo to grow.

THE NOVEL APPROACH

For a few years, infertility specialists had trouble in deciding when and in which patients to use the agonist trigger. Then, in 2011, P. Devroey *et al.* came up with the idea of an OHSS-Free clinic by using the segmentation approach. This approach involved 3 segments – 1st: Stimulation by using the antagonist protocol and trigger by GnRH agonist. 2nd: Vitrification of the embryos formed. 3rd: Embryo transfer using a frozen embryo transfer cycle. This method was gaining popularity as the chances of developing OHSS were almost completely eliminated and we were also able to transfer the embryo in a suitable receptive endometrium. There are many studies which show that COS affected the genes in the endometrium and altered it in some way. An article by Jose Antonio Horcajadas *et al.* showed that COS caused different expression in over 200 genes in the endometrium! Success in IVF depends upon quality of embryo, embryo-endometrial interaction, and endometrial receptivity, the latter two being benefitted by this technique.

THE FREEZE FEVER

Due to the evolution of cryopreservation techniques and better post-thaw survival rates, change in stimulation protocol to antagonist cycles and the inevitable increase in pre-implantation genetic testing, elective segmentation was being used for multiple purposes. In hyper-responders for eliminating OHSS, to improve endometrial asynchrony in patients with high progesterone levels, in low responders for the purpose of pooling embryos, for doing genetic testing on embryos like in PGT cycles and even for the purpose of social freezing.

Then came the meta-analysis by Matheus Roque *et al.* in 2013 which included 3 trials and had more than 600 patients which compared fresh and frozen cycles. It reported significantly higher implantation, clinical pregnancy and ongoing pregnancy rates by performing FET. But then, this study had some flaws as one of the trials had been retracted due to methodological reasons and only one study was done for normal responders, that too with only 137 patients. So the meta-analysis was also considered not valid. But by then, the

frozen fever had already started.

THE REAL PICTURE

Later, many articles were published regarding the use of this method in high responders, like the one published by Chen *et al.* in the New England Journal of Medicine in 2016, which showed better pregnancy rates using FET. Then a Cochrane review article by Wong KM *et al.* in 2017 comparing the fresh versus frozen transfer cycles gave the real picture. There was no significant improvement in the clinical pregnancy rate per woman, ongoing pregnancy rate per woman or the cumulative live birth rate per woman by using a frozen transfer cycle. Two more recent RCTs by Lan Vuong *et al.* (782 patients) and Yuhua Shi *et al.* (2157 patients) showed no significant difference in the live birth rates (31.5% vs 33.8%, p-0.54 and 50.2% vs 48.7%, p-0.50 respectively).

THE CONFUSION

In 2019, D. Wei *et al.* published an article in The Lancet which showed the a frozen single blastocyst transfer resulted in a higher singleton live birth rate than a fresh single transfer (50.4% vs 39.9%, p<0.0001), but it also showed an increased incidence of pre-eclampsia after a frozen transfer. This started the confusion and doctors began to favour frozen cycles.

THE COMPLICATIONS AND PROBLEMS

On top of the other manipulative procedures in ART, cryopreservation has a high impact on biological material and hence concerns have been raised about the health of children developed from cryopreserved embryos. Papers started to come up by now about the adverse outcomes which were associated with the use of a frozen transfer. Matheus Roque et al. mentioned the potential disadvantages of using an FET cycles like increased risk of macrosomia, hypertensive disorders and placenta accreta. In 2018, Sine Berntsen et al.11 showed that the incidence of having a large for gestational baby increased 1.5 fold by using FET compared to 1.3 fold in a fresh transfer. The risk of macrosomia also increased significantly by 1.7 folds in a FET pregnancy. Some articles state the role of estrogen in priming of the endometrium being responsible for the increased risk of hypertensive disorders, but the study by Wei *et al.* in 2019 showed a 3.1 times more risk of pre-eclampsia in FET and in this study about 62% patients had a natural cycle FET.

Everything is focused on the effectiveness in terms of prevention of OHSS, better pregnancy and live birth rates and adverse pregnancy and perinatal outcomes, but what about factors like time to pregnancy and the cost of a pregnancy? No papers have reported the time to pregnancy (defined as the time between the first day of the LMP and clinical pregnancy), but it is obvious that the time increases by at least 1 more cycle. Incremental costs are expected in elective cryopreservation due to expenses associated with cryopreservation, extra workload, endometrial priming and monitoring before FET.

A SWAT analysis by C. Blockeel *et al.* in 2016 suggested that freeze-all for all patients could not be advocated yet. A very recent article by C. Blockeel *et al.* in Human Reproduction in 2019 also suggested the same. As the long term effects of cryopreservation of embryos on the children born are still unknown and also the adverse pregnancy events caused by this are unclear, freezing should be individualized and not used in all patients.

Pros, Cons and Indications of eFET:

PROS	CONS	GREY AREA
Reduction of OHSS	No long term data on safety in terms of cardiovascular and metabolic health of the child	Pregnancy and live birth rates
Ease of scheduling a cycle	Increased risk of macrosomia, LGA, hypertensive disorders in pregnancy, placenta accrete	Time to achieve a pregnancy versus cost effectiveness
Better endometrial receptivity Reduced rates of ectopic pregnancy, placenta previa, preterm deliveries.	Increased cost	

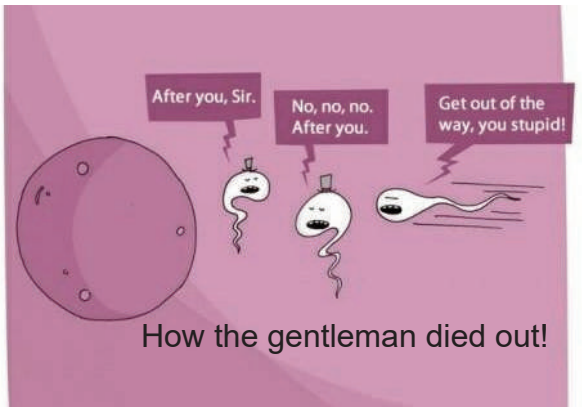
INDICATIONS FOR FREEZE-ALL

NON-ELECTIVE INDICATIONS	ELECTIVE INDICATIONS
Hyper-responders / PCOS patients for reducing risk of OHSS	Pre-implantation Genetic Testing of embryos
Endometrial / Tubal / Uterine factors	Poor-responders for pooling
Progesterone rise	Endometriosis / Adenomyosis

TAKE HOME MESSAGE:

- More long-term randomized studies on effect of vitrification (maternal and fetal)
- Ideal laboratory conditions for best outcome of vitrified embryos
- Meta-analysis showing consistent findings of the benefits of FET

For now, Freeze-all is still not for all.



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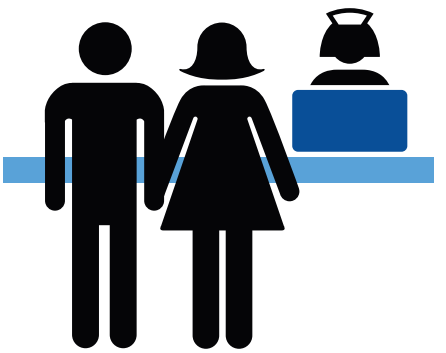
RI Witness™

Ensuring maximum security during assisted reproduction treatments

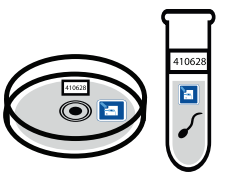
AT RECEPTION

Each person receives a unique personal code



Each couple is assigned a card with their unique personal code

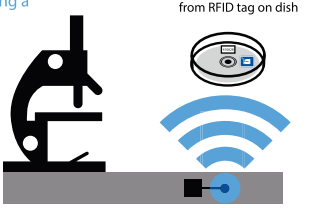
TRACKING SAMPLES

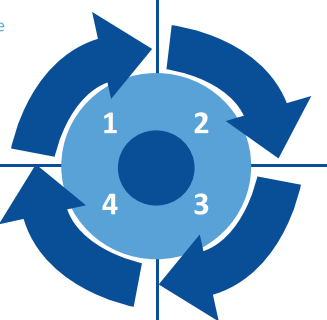


RI Witness™ RFID tags allow us to identify, track and record patient samples at each step of the ART process

Every work area in the lab detects wireless signals from these RFID tags, ensuring a secure cycle record

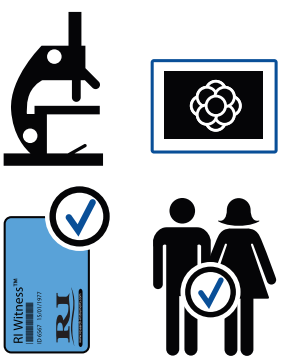
Wireless signal detected from RFID tag on dish





TRANSFER

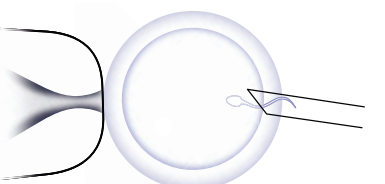
The female recipients ID card is automatically checked against the embryos prior to transfer

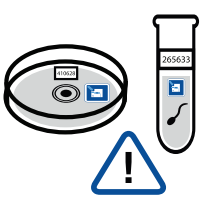


RI Witness™ is an indispensable ART management and security system which enables the IVF clinic to offer an advanced service to patients.

INSEMINATION

RI Witness™ validates the identity of the samples and allows the embryologists to proceed to insemination





In the unlikely event that samples are misidentified, the system interrupts the process preventing any potential errors

Those samples frozen and not transferred remain identifiable at all times

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FEMALE GENITAL TUBERCULOSIS AND INFERTILITY

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INTRODUCTION

Tuberculosis, caused by Mycobacterium tuberculosis (MTB) is primarily a pulmonary infection. Secondary infection may occur in any organ of the body, genital TB being one of the most common extrapulmonary manifestations. India continues to be one of the highest burden countries for TB. Female genital TB (FGTB) occurs most often due to haematogenous spread from the primary source. Rarely, ascending infection and lymphatic spread has been documented. An understanding of the contemporary scenario of diagnosis and management is important as FGTB has important implications for female reproductive health.

CLINICAL MANIFESTATIONS:

The commonest manifestations of FGTB are menstrual disturbances and / or pelvic pain. Importantly, the infection may remain undiagnosed unless actively looked for. Index TB guidelines (India) highlight that infertility itself, may be the sole presenting symptom of FGTB. The spectrum of injury to the pelvic organs varies from extensive structural and functional pelvic organ damage to an apparently normal genital tract on endoscopic examination. FGTB accounts for 3-16% of infertility in women. However, the incidence is believed to be higher than reported, due to diagnostic challenges and a large reservoir of latent infection.
The relative frequency of involvement of different parts of the genital tract and the varied clinical manifestations thereof are presented in Table 1.

Anatomical part of genital tract	Frequency of involvement	Clinical presentation
Fallopian tubes	90-100%	Pelvic pain, dysmenorrhoea, tubal blocks, hydro/pyosalpinges, peritubal adhesions, tubo-ovarian masses
Endometrium	50-60%	Menorrhagia, scanty menstrual loss, secondary amenorrhoea, intrauterine adhesions or atrophic endometrium
Ovaries	20-30%	Peri-ovarian adhesions, poor ovarian reserve
Uterine cervix	5-15%	Intermenstrual or postcoital bleeding, ulcerative or exophytic lesion on cervix
Vagina and vulva	1%	Vaginal or vulval lesions, pain or irregular bleeding.

Table I: Organ of Involvement and associated features

Latent genital TB:

Latent tuberculosis refers to clinically quiescent TB, not detected through conventional diagnostic modalities. It is important to note that latent GTB is not an inert condition. It is understood that the body mounts an immune reaction to the bacteria and prevents the active disease. However, the local immune reaction does affect the functioning of the organ affected. Another important characteristic of latent TB is its non-culturability. There is a large reservoir of latent infection in FGTB as is the case with most of the extrapulmonary TB (EPTB). It has a 5% lifetime risk of becoming active, which increases further in those with diabetes or with altered local or systemic immunity.
Table 2 highlights the reproductive implications of FGTB. While uterine, cervical and tubal damage are visible as structural damage, ovarian damage appears to be predominantly functional, noted even in latent GTB.

Endometrium	- Asherman's syndrome (intrauterine adhesions or intractably thin endometrium), - Recurrent pregnancy loss, - Recurrent implantation failure in IVF/ICSI - Irreversible uterine factor infertility necessitating surrogacy
Fallopian tubes	- Ectopic pregnancy - Unilateral or bilateral tubal blocks - Need for clipping or excision of hydrosalphinges - Need for IVF
Ovaries	- Poor ovarian reserve - Need for increased doses of gonadotropins for ovarian stimulation - Low oocyte yield and suboptimal embryo quality - Lower than expected success rate in IVF
Cervix	- Cervical stenosis - Difficult IUI - Difficult embryo transfers

Table 2: Reproductive implications of FGTB

Diagnosis:

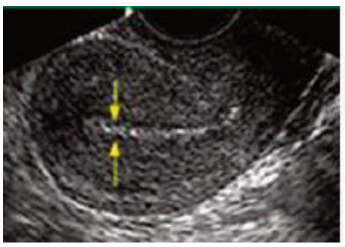
FGTB is a paucibacillary condition and most of the diagnostic tests utilized have the shortcoming of suboptimal sensitivity. The difficulty is compounded by latent GTB, which is characterized by non-culturability. The tests used in the diagnosis of FGTB are described below:

Immunological Investigations:

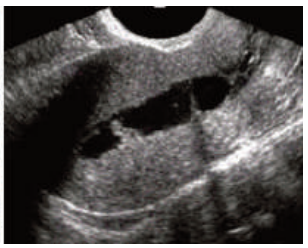
Mantoux Test: Delayed hypersensitivity reaction with induration >15 mm after 72 hours has been

used to identify those possibly suffering from TB. However, it is fraught with low specificity and sensitivity, as it cannot distinguish TB from atypical mycobacterial infections and has high false positivity in populations with a policy of universal BCG vaccination.
WHO has mandated that no serological tests should be utilized for diagnosis of FGTB. Hence both TB ELISA and Quantiferon Gold (Interferon γ) should not be used for diagnosis of FGTB.

Radiological Investigations:
Transvaginal Ultrasonography (TVS): It helps identify features highly suggestive of FGTB – persistently thin endometrium in the absence of other etiologies, persistent fluid in endometrial cavity, unilateral or bilateral hydrosalpinges, and adnexal masses.

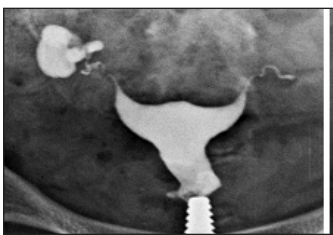


Thin Endometrium

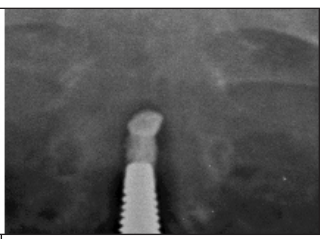


Intrauterine adhesions with fluid in endometrial cavity

Hysterosalpingography (HSG): HSG has been a valuable tool in the diagnosis of structural damage caused by FGTB. Abnormal findings include unilateral or bilateral cornual blocks, hydrosalphinges, pooling of contrast around fimbrial ends due to peritubal adhesions; intrauterine filling defects or contracted uterine cavity suggestive of intrauterine adhesions; irregular or serrated endometrial margins suggestive of endometritis; and stenosed cervical canal.

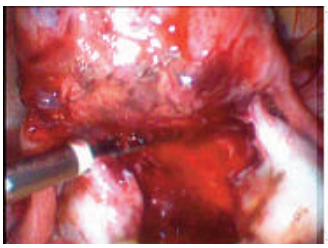


Bilateral tubal block with Right hydrosalpinx

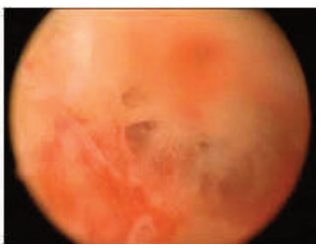


Severely contracted uterine cavity (Asherman's Syndrome)

ENDOSCOPIC ASSESSMENT:
Laparoscopy is considered as the gold standard for clinical diagnosis of FGTB. The features are well recognised – tubercles (localized or widespread on peritoneal surfaces), adhesions, oedematous /tortuous / lead pipe like tubes, conglomerated fimbriae, hydrosalpinges, tubal blocks; shrunken ovaries / ovarian abscess / tubo-ovarian mass and perihepatic adhesions. Hysteroscopic findings include thin, bald, atrophic endometrium; intrauterine adhesions; tubercles and ulcerative endometrial lesions.



Laparoscopic view of tubercles and extensive adhesions



Hysteroscopic view of intrauterine adhesions and pale endometrium

HISTOPATHOLOGICAL EVALUATION:
An endometrial biopsy may reveal granulomatous lesions with caseation. However, this is a rare occurrence due to cyclical shedding of endometrium preventing a typical granuloma from developing.

Microbiological Assessment:
Microscopy: Presence of AFB under microscopic examination of any of the tissue or body fluids confirms the diagnosis, but is rarely the case as FGTB is paucibacillary in nature.
Bacteriological Culture: Identification of the bacteria in endometrial tissue sample confirms the diagnosis. Traditional culture in Lowenstein Jensen medium takes 6 weeks for confirmation of infection. The BACTEC 460 or BACTEC MGIT 960 liquid culture provide results within 14 days and reduce the time to diagnosis.
Index TB guidelines sets the diagnostic criteria for FGTB as: Laparoscopic findings of GTB **OR** tissue biopsy positive for AFB on microscopy or M TB on culture OR histopathological findings consistent with TB.
Molecular Diagnosis: Paucibacillary nature and latent infection both pose important hurdles for bacteriological diagnosis. Molecular diagnostic methods are useful for diagnosis of FGTB under such circumstances (Table 3). WHO recommends the used of Nucleic Acid Amplification Tests (NAATs) for the diagnosis of EPTB. DNA PCR is the most widely used test for the diagnosis of FGTB while the use of RNA PCR is restricted as it requires an in-house laboratory and immediate processing of the sample.
Use of multiplex DNA probes further improves the sensitivity and specificity of the tests when compared against a composite reference standard (CRS). 'Index TB guidelines' acknowledges the usefulness of molecular diagnostic tests in the context of FGTB.

Test	Lower Limit for detection
AFB smear and microscopy	1000 bacilli/ml
Bacterial culture	100 bacilli/ml
PCR	1-5 bacilli/ml

Table 3: Minimum bacterial load required for diagnosis by various methods.

Endocrine Evaluation:
Reduced ovarian reserve markers such as AMH and AFC in young women should raise the index of suspicion for FGTB, as oophoritis or ovarian damage cannot be diagnosed by TVS or laparoscopy.

WHOM SHOULD WE TEST?
There is a growing concern that infertile women are over-tested and over-treated for FGTB. Defining a subset of women in whom histopatholgical / bacteriological / molecular testing for FGTB should be performed remains a challenge. Conversely, delaying the testing may lead to irreversible damage to the reproductive organs. Hence, in the absence of a clear consensus, women fulfilling the following criteria may be considered for testing:
1. Those with any form of female infertility of at least two years' duration, which has not responded to standard form of fertility treatment.
2. Findings on radiological investigations (USG and HSG) suggestive of TB.
3. Laparoscopic and hysteroscopic findings suggestive of TB.
4. Those with unexplained early reduction in ovarian reserve (low AMH and AFC).
5. Those with recurrent pregnancy loss and / or recurrent implantation failure in IVF.
It has to be noted that FGTB is almost exclusively caused by M tuberculosis. However, an increasing practice of consuming unpasteurized milk from sources with no preventive programme implemented for bovine TB can lead to resurgence of M bovis infection as well.

MANAGEMENT:
Management of FGTB is multidisciplinary. Structural and anatomic disturbances are treated surgically during laparohysteroscopy. Once the diagnosis is confirmed, it is important to advice evaluation by a pulmonologist or physician to evaluate for any concomitant active primary source of infection. Antituberculous treatment (ATT) involves 'standard ATT' for six months. While pregnancy should preferably be avoided during the first two months of treatment (intensive phase), nearly 50% of those who achieve pregnancy will do so during the following four months. Counseling and supervision is important to ensure adherence to treatment, identify drug induced side-effects; prevent drop-outs and occurrence of multi-drug resistant TB; and for adequate psychological support.

CONCLUSIONS:
Female genital tuberculosis is a spectrum encompassing latent to clinical disease. It has high prevalence in our infertile women and the diagnosis is challenging. Meticulous evaluation and appropriate treatment mini

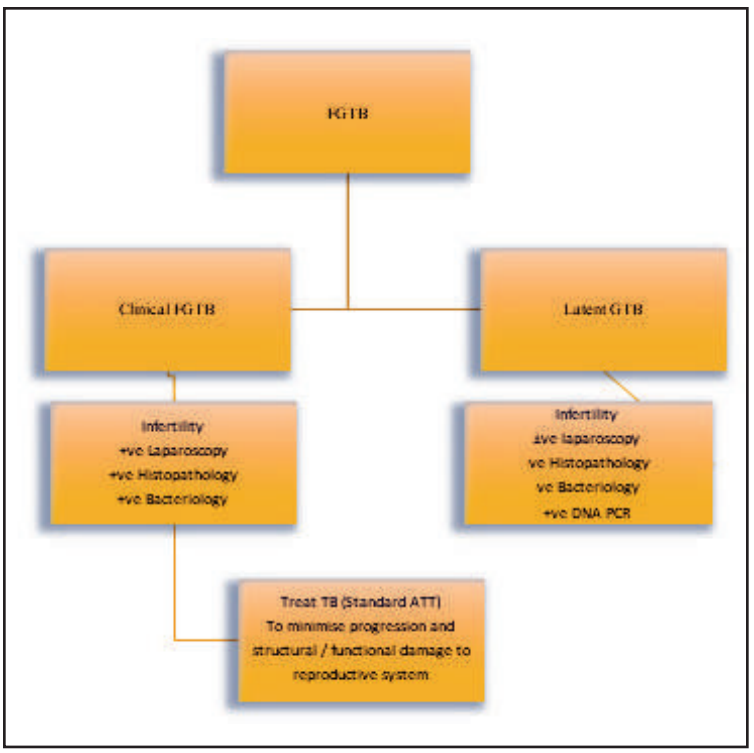
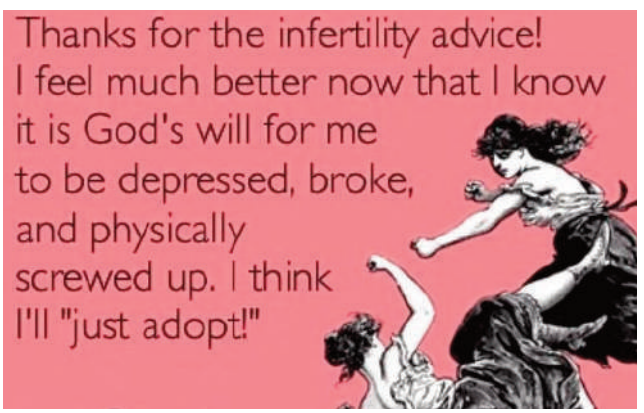


Figure 1: Spectrum of Female Genital Tuberculosis

mise the risk of permanent infertility and improve the occurrence of successful pregnancies in such women.

TAKE HOME MESSAGE:
• FGTB is a common cause of not only tubal factor infertility but also of uterine and ovarian factors.
• Evaluation is challenging and is based on a combination of clinical, radiological, endoscopic criteria.
• Histopathological or bacteriological diagnosis is important.
• However, latent GTB can only be diagnosed by molecular methods (Choose appropriate test and facility).
• Treatment of infection is standard ATT under appropriate supervision followed by treatment of infertility.



OVARIAN REJUVENATION

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INTRODUCTION:
The age of motherhood is creeping up, and more women are having children in their 40s than ever before. On contrary Primary ovarian insufficiency (POI) affects around 1%–3% of women of the reproductive age group and about 0.1% in women below 30 years of age (ESHRE 2016; Fenton, 2015; Pouresmaeili and Fazeli, 2014). New oocytes do not develop in these women under normal circumstances. Woman is born with all the oocytes that will be available for conception during her reproductive life. Woman's supply of oocytes diminishes both in number and genetic quality as she ages. "Is there a hope that menopausal women will be able to get pregnant using their own genetic material".
Ovarian rejuvenation is a procedure that may create new oocytes in the ovaries of women who are unable to conceive because of early menopause, advanced maternal age or low oocyte reserve, yet who wish to have their own biological child. A significant proportion of these individuals are either unable or unwilling to use donor eggs or to adopt a child. Most of the approaches of ovarian rejuvenation is aimed at activation of residual primordial follicular pool or the resting ovarian stem cell by supplementing the niche. The present review is aimed at elaboration and critical evaluation of various approaches to ovarian rejuvenation and their outcome.

APPROACHES TO OVARIAN REJUVENATION:
Autologous platelet rich plasma: It is offered for the following women, a) Menopausal or perimenopausal women under 50 years, b) low ovarian reserve, c) Low Anti-Mullerian Hormone (AMH) levels, and d) Premature ovarian Insufficiency (POI). Autologous activated PRP is prepared by collecting 17.5 ml of patient's own blood and mixed with 2.5 ml of ACD-A solution and processed by two step centrifugation method and activated by calcium gluconate. This would result in release of molecular mediators such as IL-1β, IL-8, PF4, VEGF, PDGF etc. from alpha granules. These factors may trigger differentiation of ovarian stem cells (OSCs). It is injected intraovarian by TVS guidance using 17G ovum aspiration needle or laparoscopically by using an amniocentesis needle passed through veress needle inserted suprapubically under vision.
In women with amenorrhea it can be injected anytime, but in menstruating women it is injected in the early follicular phase. Following PRP injection ovarian reserve tests (FSH, LH, E2, AMH, AFC) are repeated monthly, and menstruation is expected to resume within 6 months in successful cases. PRP can also be used as an alternative to hormone replacement therapy and delay menopausal symptoms such as hot flushes, skin changes, cardiovascular and bone health.
Benefits and Risks: This is an innovative procedure and considered experimental. The benefit of this procedure is the possibility of achieving pregnancy spontaneously or with patient's own oocytes by ART. The risks are minimal which include pain, fever or internal bleeding in rare cases.

Outcome of intraovarian PRP: Sills et al reported a series of four women with ovarian insufficiency aged >35 years with previous IVF failure. Post-PRP injection there was an improvement in mean serum FSH and AMH levels. They underwent COH with ICSI all the four patients had at least one blastocyst. Embryo transfer was performed in one patient which resulted in a positive ongoing pregnancy at 9 weeks (Sills et al., 2018; Sills and Wood, 2019). Sfakianoudis et al performed intraovarian PRP in three women of advanced age (>35 years) and poor responders. Of them one conceived spontaneously and two by frozen embryo transfer. One woman had a successful live born baby and two ongoing pregnancies at 17 and 24 weeks (Mogharbel et al., 2017). Sfakianoudis's team announced that it had offered intraovarian PRP to 30 infertile women between the ages of 46 and 49, and successfully retrieved oocytes and obtained embryos from most of them. They claimed that this therapy would work in about two-thirds of cases of ovarian insufficiency.

Peripheral blood mononuclear cells (PBMC):
Herraiz et al were the first to report autologous stem cell ovarian transplantation (ASCOT). G-CSF is administered at a dose of 10 µg/kg/day for 5 days and stem cell collection is performed if patients reached a threshold of CD34+ circulating cells in peripheral blood ≥10 cells/µL. Cell collection is performed by continuous flow apheresis in a cell separator. The target was to reach a minimum of 4 × 106 CD34+ cells/kg. About 50 × 106 CD133+ cells are delivered into the ovarian artery by the intra-arterial catheter into one ovary. Herraiz et al performed this procedure in 15 poor responders with previous failed IVF. There was

significant improvement in AFC from 4.0 ± 1.3 (4.0) to 4.9 ± 2.2 (5.0). Of 28 ART cycles performed in them, oocytes were obtained in 85.7% (24 of 28) of cycles. Two women of the 17 transferred, conceived (11.7%). One pregnancy ended in miscarriage and one woman delivered successfully. Three women conceived spontaneously, of which two had successfully delivered healthy babies (Herraiz *et al.*, 2018a).

Ovarian stem cells: In contrary to the older belief that follicle number in a female is finite, White et al and Jonathan Tilly at Harvard Medical School, first isolated ovarian stem cells (OSCs) in adult human female. These cells showed in vitro, their potential to grow into oocytes. This area of science needs to be explored in future research, and could evolve as a promising treatment for women with premature ovarian failure (White *et al.*, 2012).

Autologous Bone-marrow derived stem cell injection: The interactions between bone marrow derived stem cells (BMDSCs) and ovarian hormones have been noted in animal experiments. Ovariectomy resulted in increase of ProB/ Precursor B cells (bone marrow derived stem cells) and combined ovariectomy with thyroidectomy increased MSCs in rats thus depicting the possible role of bone marrow derived stem cells in tissue regeneration and repair, pertaining to ovary (Mogharbel *et al.*, 2017). In this method about 120 ml of bone marrow was aspirated by 13G Jamshidi needle on a heparinised 20 ml syringe. 16 ml of BMDSC suspension was obtained by using the Sepax cell separator and were instilled into both ovaries at 3–4 sites laparoscopically. Gupta et al achieved the world's first pregnancy by bone marrow derived stem cell therapy in a 45 year old perimenopausal woman (Gupta et al., 2018). The mononuclear cells and growth factors in the stem cell preparation is known to stimulate the residual follicles and successfully grow them to the hormone sensitive secondary follicles, thereby making them responsive to ovarian stimulation (Herraiz *et al.*, 2018b).

Mesenchymal stem cells (MSCs): Mesenchymal stromal cells, are nonhematopoietic adult stem cells that originate from the mesoderm. They possess self-renewal abilities and multilineage differentiation into mesoderm lineages, such as adipocytes, chondrocytes, osteocytes, and ectodermic and endodermic cells (Zhao *et al.*, 2019). They are classified based on their source: Bone marrow derived stromal cells, Adipose-derived stem cells, Menstrual Blood Mesenchymal Stem Cells (MB-MSCs), and Umbilical Cord Mesenchymal Stem Cells. They have been used in animal models to treat ovarian dysfunction, and in humans to treat thin endometrium (Zhao *et al.*, 2019). As they have greatest advantage of ease of obtaining and are autologous in nature, their use may be promising in ovarian rejuvenation in future.

Autotransplantation of ovarian cortical tissue: This was originally performed as a method of fertility preservation for cancer patients undergoing chemoradiation. In this ovarian tissue is harvested laparoscopically and Ovarian cortical tissue is harvested. Ovariectomy is avoided unless the chemotherapy is expected to cause >50% of ovarian damage. A huge chunk of ovarian cortex is harvested, or alternatively small 5cm slices of 4-5 were harvested from each ovary and cut into 10 x 1.5 mm slices and vitrified. Vitrification is highly efficient in terms of follicular survival and outcome. The warmed ovarian cortical strips after thawing are quilted together with a 9-0 nylon sutures and applied to the denuded ovarian medulla. Multiple micro-pressure interrupted stitches were taken by 9-0 nylon. Silber et al performed ovarian auto transplantation in 13 patients. All patients resumed menstruation, in 4-5 months. Of these patients 9 (69%) patients delivered a total of 13 live born babies, with one miscarriage (10%)(Silber *et al.*, 2018).

Ovarian fragmentation for follicular activation (OFFA): Kawamura et al described the role of disruption of Hippo signalling on ovarian germ line stem cell (OGSC) proliferation and differentiation. Ovarian fragmentation caused disruption of Hippo signalling by actin polymerization and increased nuclear YAP levels. This further activated the downstream pathway of CCN growth factors and BIRC apoptosis inhibitors (Kawamura *et al.*, 2013). Part of the ovarian cortex was removed by laparoscopy, sectioned into small cubes (usually >80 small pieces) and replaced back to its anatomical location by tunnelization. The procedure has been called Ovarian fragmentation for follicular activation (OFFA) and so far, 4 pregnancies out of 14 early menopausal women have been achieved. Overall, 87 live births and 9 on going pregnancies were reported by this procedure, all over the world, and the pregnancy rate following this procedure is about 30% (Kim *et al.*, 2018).

SUMMARY

Stem cell transplantation is an evolving science in reproductive biology and considered experimental. Various applications of stem cells in reproductive biology include Asherman syndrome, thin endometrium, ovarian insufficiency and non-obstructive azoospermia. The role of stem cell therapy in ovarian rejuvenation is mainly aimed at the activation of residual follicles, and is less likely to work in the presence of severe pathology such as genetic causes (Turner syndrome, Fragile X syndrome), immunological and drug induced(chemo- radiation). The major challenge with stem cell transplantation is occurrence of angiogenesis to facilitate their proliferation, survival and differentiation.

CONCLUSION

Stem cell therapy like in other branches of Medicine is going to revolutionize the Reproductive Medicine as well. Ovarian Rejuvenation is a possibility, and we need further research with randomized studies to support this finding.

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IS MTP LEGAL BEYOND 20 WEEKS ?

MTP AFTER 20 WEEKS IN TWINS PREGNANCY: First case in the History in Indian Judiciary

INTRODUCTION

The diagnosis of infertility in itself is the common denominator for the increase in the rates of anomalies seen in both ART and spontaneous conceptions.

In this era of assisted reproduction multiple fetuses have become a common occurrence and getting one foetus with some major anomaly is not a far-fetched consequence. There are various circumstances when these anomalies are not diagnosed before 20 weeks or they do appear late and when they become visible it's a big ethical and legal dilemma for the clinician and couple for its right course of action. The following case published by Dr. Nikhil Datar is an interesting and useful evidence in such case scenario.

Mrs X (name withheld) came with peculiar situation as under:

1 Mrs X had dichorionic diamniotic twin pregnancy. Due to sub-chorionic Haemorrhage her dual marker test was not done. Her previous Obstetrician had performed quadruple marker which showed high risk for aneuploidy. Amniocentesis revealed that one of the foetuses had trisomy 21.

2 By the time the confirmatory report came she had crossed the legal limit of 20 weeks as per MTP Act.

3 By the time she was referred for further management she was already 23 weeks pregnant.

4 She was counselled for three possible treatment options:

• Give birth to both the babies and accept the trisomy 21 baby.

• Do termination of pregnancy for both the foetuses after seeking the permission from the court.

• Do selective foetal reduction of the trisomy 21 foetus with acceptance of due risk of the procedure after seeking the permission of the court.

5 Mrs X declined to accept the first option. Although she was keen on selective feticide and continuation of pregnancy with normal foetus, but no one was sure if the court would allow foetal reduction especially after 20 weeks.

It was decided to file a writ petition in the Bombay High court. The high court referred the matter to the medical board at J J Hospital (Government medical college in Mumbai) on 15th May 2020. Based on the report of the JJ Hospital, the High court denied permission for termination of pregnancy.

An appeal was made against the impugned order to the Supreme Court and point was brought to the notice of the apex court that the committee of

doctors at JJ Hospital did not have foetal medicine subspecialist. The apex court directed JJ hospital to include foetal medicine subspecialist and review its report. The foetal medicine specialist's opinion was a game changer. On the basis of that report the apex court gave final order permitting termination of pregnancy by performing selective feticide. The same was performed by Prof. Dr Poornima Satoskar at Nowrosjee Wadia Hospital and finally the mother had delivered a single, normal live baby later.

This is the first ever feticide performed after 20 weeks in multi-foetal pregnancy after specific permission from the apex court.

This case raises following questions:

1. Can MTP be performed after 20 weeks?
2. What is the procedure for the same?
3. How does one conclude about seriousness of abnormality in the foetus when it is not a lethal anomaly?
4. Is ultrasound guided feticide legal?
5. Does feticide in multiple pregnancies mean to be termination of pregnancy?

Here are the answers:

1 Can MTP be performed after 20 weeks?

Yes. As per the writ petition of Dr Nikhil Datar Vs Union of India in the Hon'ble Supreme court demanding upwardly revision of the limit of twenty weeks for termination of pregnancy. In Miss X and Dr Nikhil Datar Vs Union of India (2006), the apex court ordered termination of pregnancy at 24 weeks.

Since then, Dr. Datar helped nearly 150 women to approach the courts, when their pregnancies had gone beyond 20 weeks cut off and nearly all have got permissions to terminate their pregnancies.

It must be mentioned that courts have only permitted abortions when women has had a seriously malformed foetus or when they were victims of sexual assault and of minor age.

Finally in March 2020, the amendment to the MTP Act has been passed in Lok-sabha. Yet it has not been passed in Rajya-sabha. Till such time the bill is not formally passed and notified, women will have to approach respective high courts to seek permissions. Needless to say, the procedure has now become streamlined and average tune around time has been just around 10 days.

2 What is the procedure for the same?

I. The woman approaches the high court and files a writ petition. The women provides the medical opinion that should specify following:

a. That she is beyond 20 weeks of pregnancy and has foetal abnormality that is substantial and serious in nature.

b. That risk of termination to the woman at this stage is not higher than that of delivery. (There sufficient medical evidence to this)

c. That woman on her own accord wants to terminate the pregnancy.

II. The High Court directs the woman to permanent medical board set in the state. (Usually the government medical college in that state).

III. The committee provides the report. Based on the report the court orders for termination of pregnancy.

3 How does one conclude about seriousness of abnormality in the foetus when it is not a lethal anomaly?

In this case Dr Nikhil Datar Vs Union of India, the union government has filed an affidavit which includes "guidelines for medical boards". This guideline has enlisted large number of anomalies to be considered as "substantial and serious". These anomalies include trisomy 21 to heart abnormalities. Thus it is clear that termination is not only restricted to lethal abnormalities before as well as after 20 weeks cut off.

4 Is ultrasound guided feticide legal in India?

It is evident from the above mentioned case that foetal reduction after 20 weeks is legitimate provided that the court has approved of the same. The guidelines from the ministry have mentioned that feticide may be done when termination is planned after 24 weeks so as to avoid live birth.

5 Does foetal reduction in multiple pregnancies mean to be "termination of pregnancy?"

The MTP Act or law in general is unclear on the interpretation.

Some believe that feticide is not covered under the MTP Act. The argument put forth is as under:

In multifetal pregnancies, even after the foetal reduction is done, the pregnancy continues. Hence one can conclude that the said procedure is not covered under the termination of pregnancy Act.

However I am of the view that termination of pregnancy is to be equated to abortion and plain meaning of the words should not be taken into consideration.

Thus author advises to have cautious approach till legal clarity is brought in.

Conclusion:

The law needs to evolve in accordance with the advances in medical science. Judicial activism is the way forward to innovate in the field. Ensuring legal compliance makes the MTP medico-legally safe for the doctor because any slightest deviation from the MTP Act may directly attract criminal proceedings under Indian penal code.

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Chairperson

Dr. Nivedita Shetty
Hony Secretary

Dr. Lavanya Kiran
Hony Jt. Secretary

Dr. Shashikala K.T.
Member

Karnataka State Chapter Contribution

ROLE OF GONADOTROPINS IN IUI

Intrauterine insemination (IUI) is often the first-line procedure in assisted reproductive technologies (ART) due to its simplicity and low cost. IUI combined with COS increase the cumulative pregnancy rate. The most commonly used medications are CC, Letrozole and gonadotropins. Gonadotropins are associated with a higher live birth rate as compared to clomiphene and Letrozole, however the draw backs are, it is expensive and are associated with higher incidence of multiple pregnancy and OHSS.

INDICATIONS
- Hypogonadotropic Hypogonadism
- Clomiphene / Letrozole -Resistant anovulation
- Unexplained Infertility
- Advanced age

Hypogonadotropic Hypogonadism (WHO Group I)
Drug of Choice is Gonadotropins containing both FSH and LH

Clomiphene-Resistant Anovulation (PCOS; WHO Group II), high LH
Purified FSH preparations offer a theoretical advantage, However - there is no evidence that purified FSH has greater efficacy than hMG and either may be used

Clomiphene/Letrozole Resistant Anovulation
(PCOS; WHO Group II)
Change from CC to gonadotropins

Unexplained Infertility
The role of Gonadotropins for unexplained Infertility has been debated. A Recent systematic review and meta-analysis do not support the use of gonadotropin for
OS-IUI in women with unexplained infertility. To gain additional live births, higher dose and lax cancellation policies have to be used, thus increasing the risk of multiple gestation.

No. of follicles & preg. rate per cycle
The pregnancy rate is proportional to the number of follicles.

No of follicles	Pregnancy rate
1	6.2 %
2	12.9 %
3	30 %

Efficacy

	Hypogonadotropic hypogonadism	CC resistant anovultion
Cycle fecundity	25 %	5 – 15 %
Cumulative PR after up to 6 cyles	90 %	30 – 60 %

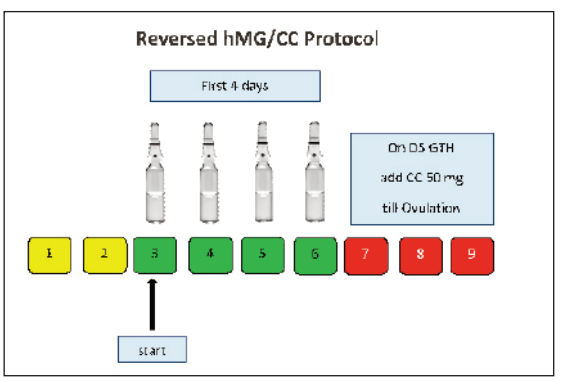
Different gonadotropins preparations available

Gonadotropins		Molecule
1st generation - hMG (Menotropins)	Post Menopausal urine	75 IU FSH and 75 IU LH 95 % urine proteins
2nd generation - Highly purified hMG		75 IU FSH and 75 IU LH <5 % urine proteins
3rd generation - (Urofollitropin) Purified Urinary FSH	LH removed with polyclonal antibodies Still contains high amounts of urinary protein	75 IU FSH and LH < 1 IU 95 % urine proteins
Highly purified FSH (HP - FSH)	Use of highly specified monoclonal antibody extract FSH	75 IU FSH and LH < 0.1 IU <5 % urine proteins
4th generation - Recombinant FSH	Genetic engineering Absent urinary protein More consistent supply	Follitropin alpha
Recombinant FSH	Less batch to batch variation in biologic activity	Follitropin beta

PROTOCOLS
A. Gonadotropins in combination with oral ovulogens
- Sequential approach

CC 50-100 mg / Letrozole 2.5-5mg from D3-D7 followed by hMG 75 IU from D7 of the cycle
- Overlapping approach

CC 50-100 mg / Letrozole 2.5-5mg from D3-D7 & hMG from D5 of the cycle
- Reversed hMG/CC Protocol



B. Gonadotropins alone

1. Step-up

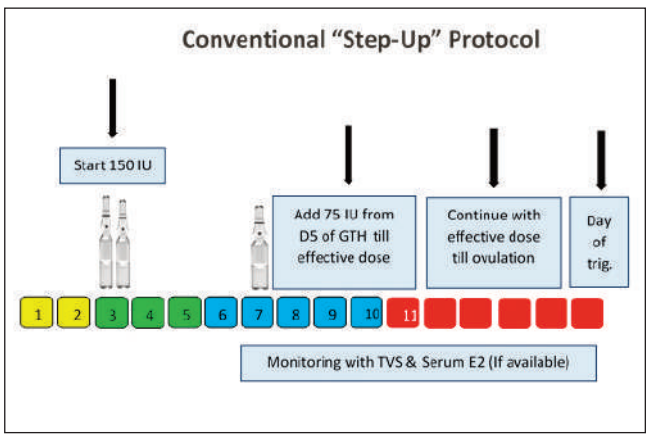
Conventional/Standard (Starting dose- 150 IU)

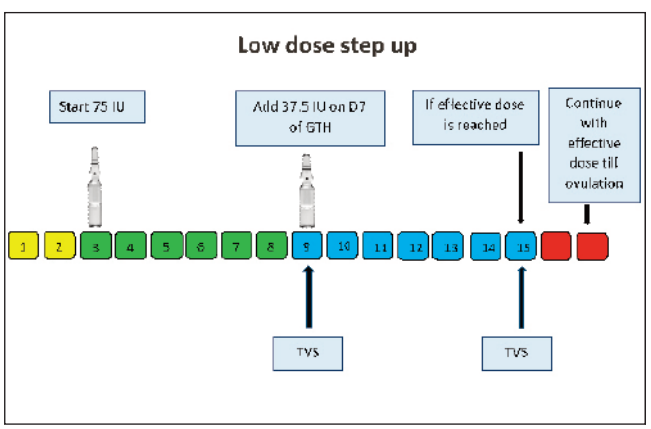
Low Dose Step-up (Starting dose- 75 IU)

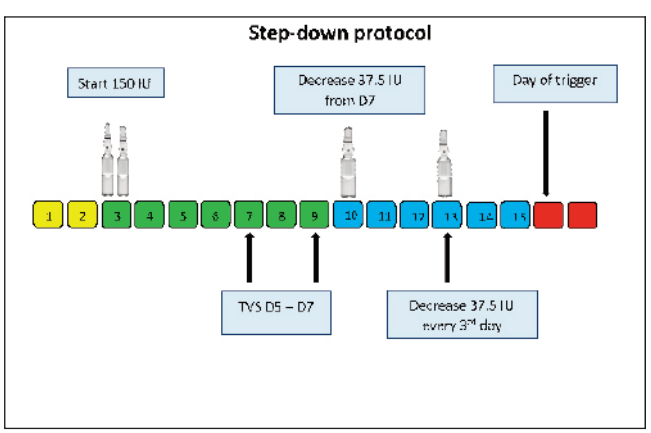
2. Step down

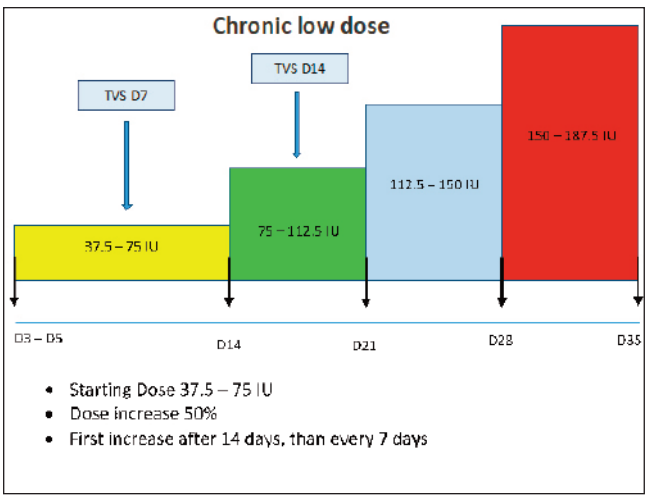
3. Chronic low dose

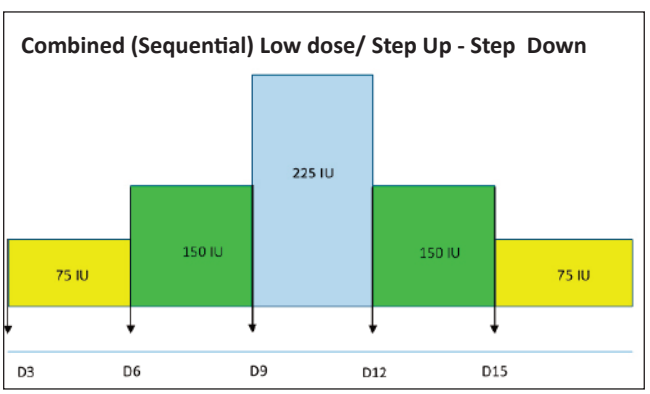
Mimics physiological progression of gonadotropins in Natural cycles











Fixed dose regimen:

Gonadotropin dose is constant throughout the stimulation which is given daily or on alternate days.

Complications

• OHSS – Can be Life threatening

Risk factors

• Young age • Low body weight

• PCOS • Higher doses of gonadotropins

• Previous episodes of ovarian hyperstimulation

• hCG • Trigger & luteal phase support

Multiple pregnancy :

Withhold HCG administration in the presence of more than two follicles ≥ 16 mm or

More than one follicle ≥ 16mm and additional two follicles ≥ 14 mm.

TAKE HOME MESSAGE

• Use of Gonadotrophins for IUI cycle is associated with a higher success rate

• Gonadotrophins must be used judiciously

• Low dose protocols are advised in women with PCOS

• Close monitoring by USG is mandatory

• Strict cancellation policy is recommended to avoid multiple pregnancy

Delhi State Chapter Contribution

MINIMISING ERRORS IN IVF LAB

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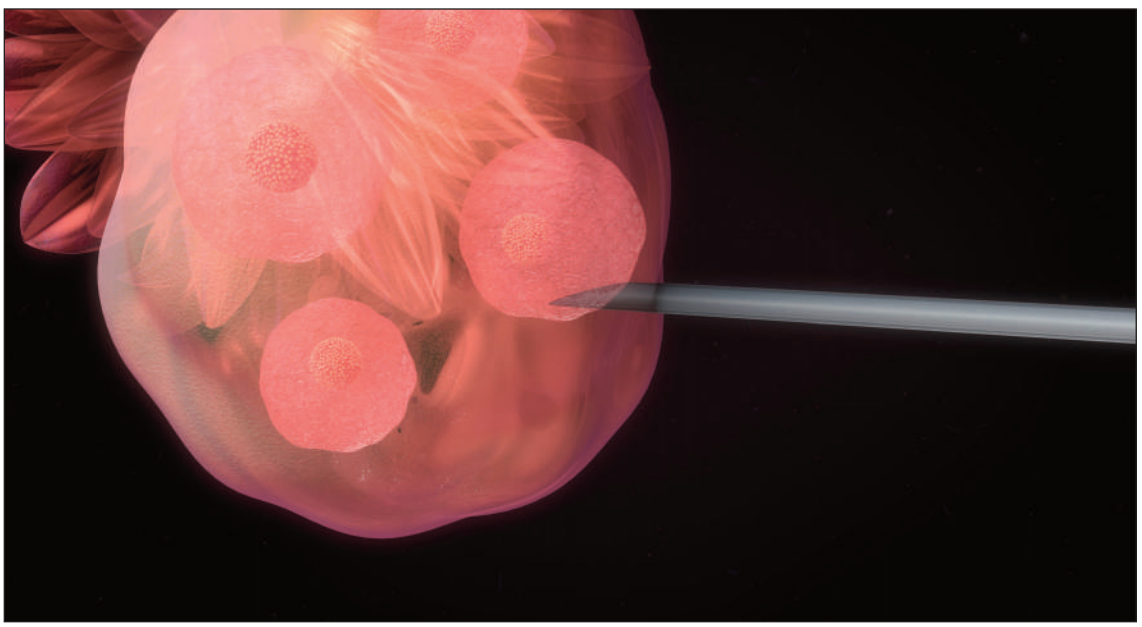

The birth of Louis Brown in 1978 marked the beginning of a new chapter in medicine : Artificial Reproductive Technology or ART. In these forty years infertility treatment has come a long way with the advent of newer technologies and advancements as well as awareness. In India, it is heartening to witness the acceptance of infertility treatment. From being a taboo subject to achieving the status of mainstream treatment procedure, ART has gained widespread acceptance in our society. In the national capital region itself, there are more than 300 ART centres and India is expected to lead the world in term of the number of IVF cycles performed per annum.

Infertility treatment, although not usually life threatening, has permanent consequences in the lives of those receiving it. There is no room for error. Having said that, humans are infallible and errors are inevitable. The errors are never intentional, but it is imperative to understand their potential origin and to adopt the protocols necessary to avoid them.

One way to understand errors is to classify them in terms of

(a) Significance and impact of the error

(b) Cause of the error

(a) Boston IVF classified the errors based on their impact in four categories :

(i) None/Minimal (not likely to decrease the chance of success)

(ii) Moderate (a negative impact but not loss of a cycle)

(iii) Significant (loss of a cycle or majority of gametes or embryos)

(iv) Major (a gamete mix-up leading to a permanent consequence for the patients and the ART facility or a complete failure of an equipment or documentation affecting multiple patients)

(b) The cause or origin of the error can be human or mechanical. The levels at which there is a potential of error are listed as follows:

(i) Embryologist/Lab technician: According to ICMR ART bill of 2017, the chief embryologist must be at least a post-graduate in life sciences or a graduate with a minimum of 5 year of human embryology experience. Skilled and qualified laboratory personnel can prevent a lot of avoidable errors in the lab. At least two embryologists with appropriate skill sets are recommended in an IVF lab. They should be thoroughly briefed and their KPI's must be continually monitored.

(ii) Quality management : Internal and external

audits must be implemented at regular intervals.

(iii) Identification of patients and traceability of their reproductive cells: The single most important priority of ART treatment is patient identification and correct allocation of gametes. Gamete mix-ups are very rare, but not entirely unheard of. It is thus imperative to employ all possible precautions to prevent any gamete mis-allocations in the IVF laboratory.

Patient identity allocation has to begin at the stage of patient registration. A unique patient ID must be assigned to each patient and that has to be adhered to in every step of the procedure. The crucial steps of the procedure are gamete handling during the day of the oocyte retrieval and insemination followed by embryo transfer. Extreme caution must be undertaken during oocyte retrieval and IVF/ICSI, by proper labeling of the dishes with the patient name and unique ID that has to be double witnessed. Only one patient's gametes must be handled at a time to avoid accidents. During embryo transfer, it is crucial to retrieve the correct embryos from the incubator and to load them in the catheter. With the advancement of technology, electronic monitoring systems are now available that label each patient with its unique bar code number or a unique radio frequency ID (RFID) number. Once the labware is labeled with these, a continuous monitoring system ensures almost zero error in patient identification. In addition to this, it is still prudent to maintain a human double witnessing system, thus eliminating any possibility of a gamete/embryo switch. Proper staffing, reduced workload and clear communication between workers is key to prevent any errors during the procedure.

Fig 1: Electronic witnessing system

(iv) Consumables: All consumables used in ART should be MEA tested and approved for human IVF laboratory use.4 All consumables should be single use and disposable. While receiving the media/disposables, proper documentation should be done regarding the batch number, expiry date and cold chain maintenance (for media).

(v) Handling of biological material : Biological material should only be handled by trained staff/technicians/embryologists. All biological material should be processed in aseptic conditions, under a laminar hood and at 37°C, in a pH of about 7.2. The gametes of only one patient should be processed at a time. Exposure to light and inappropriate temperatures must be avoided. The media should be properly equilibrated before handling or culturing of gametes.

(vi) Oocyte retrieval : the unique identification code of the patient must be recorded and confirmed before oocyte retrieval or OPU. Before the procedure the test tubes for follicular fluid collection must be pre-warmed at 37°C. A dry run to check the functioning of all equipment like aspiration pump is desirable before OPU. The oocytes should not be exposed to follicular fluid for long, so the lab should be adjacent to the OT and oocyte identification must be done quickly after aspiration. Proper labeling of the petridish with double witnessing is mandatory.

(vii) Sperm preparation : Patient should be given clear instructions regarding sample collection in terms of abstinence and hygiene. It is desirable that semen collection takes place at the IVF facility itself as opposed to home collection. Single semen sample must be processed at a time to avoid any mistakes. Appropriate semen preparation method should be applied depending on the semen quality and the technique performed (IVF or ICSI). Proper chain of identification must be maintained through labeling and witnessing.

(viii) Insemination of oocytes :

• *Conventional IVF :* For insemination, great care must be taken to prepare the semen sample to avoid any infection in the insemination dish. The concentration of sperm added should be carefully aliquoted and performed in a medium suitable for aiding sperm function and oocyte fertilization. A double check of the identity of gametes is mandatory at this point. The timing of insemination and operator name has to be noted

• *ICSI procedure :* While oocyte denudation, exposure to hyluronidase and light should be limited to a minimum. Proper lumen denuding pipettes must be employed to reduce any stress or damage to oocytes. Denudation must be performed as close to ICSI as possible since denuded oocytes are most susceptible to changes in pH.

(ix) A record should be maintained of oocyte maturity. ICSI should be performed by a skilled embryologist. Oocyte morphology must be recorded and immature/giant oocytes should not be subjected to injection. Morphologically normal sperm are most appropriate for ICSI. During injection, care has to be taken to place the polar body at 12 or 6°clock position and to ascertain that the oolemma is ruptured before depositing the sperm in the cytoplasm.

(x) Scoring for fertilization : Fertilization check should be performed between 16-18 hours post insemination and the embryos exhibiting multiple pronuclei must be discarded.

(xi) Embryo culture: The culture media must be stage specific apropos to the embryo development. In case of

sequential media, care must be taken to shift the embryos from fertilization media to cleavage stage media to blastocyst stage media chronologically. Proper labeling and double witnessing during embryo shifting is imperative.

(xii) Embryo transfer : Embryo scoring must be done not long before transfer. The number and quality of embryos to be transferred must be decided depending on patient history, embryo quality and after discussion with the patient.

Patient ID must be confirmed and informed to the lab. It is advisable for the embryologist to confirm the name of the patient and partner from the patient herself. Embryo transfer dish must be prepared not long before the transfer and labeled with the patient's name and unique ID. There must be double witnessing. While loading the embryos in the catheter, patient's name and ID should be announced loud and clear. Loading of the embryos must be done in 20-30µl of culture media, without much exposure to light. Post transfer, the catheter must be carefully checked to ensure that the embryos have been deposited in the uterus.

(xiii) Cryopreservation : All devices must be clearly and permanently labeled and the cryopreservation protocol followed rigorously. Contamination of external surfaces of cryodevices must be avoided while loading sample onto them. The details of sample loaded in/on each device must be carefully documented. There should be separate containers for storage of sero-positive samples. Vitrified samples must remain dipped in liquid nitrogen at all times, till they are ready for thawing. Various continuous nitrogen monitoring systems can now be availed of, that inform the embryologist via a text message and alarm when nitrogen levels in a cryocontainer go below an acceptable level.

(xiv) Laboratory safety and equipment: Laboratory equipment must be adequate to cater to the number of cycles performed in the ART unit. The equipment must be calibrated and serviced at least once in three months. Embryos in culture must be evenly distributed among incubators to prevent frequent opening of the incubators. Malfunctioning equipments must be clearly labeled to avoid their accidental use. The gases used must be medical grade and supplied with a certificate, especially in case of mixed gas cylinders.

(xv) Infectious agents : All patients must be sero negative for viral markers before their biological fluids are accepted in the lab. Special SOPs should be in place to handle sero-positive samples. Extreme care must be taken to process the infected samples and they preferably should be handled at a workstation separate from regular. Alternatively, patients with positive viral markers should be treated at time slots different from the other patients and all surfaces have to be thoroughly disinfected before handling any other sample.

(xvi) Protective measures : It is wise to treat all biological material as infected and to handle them with strict hygiene regulation and aseptic technique. Generation of any kind of VOC in the embryology lab is detrimental to gametes and developing embryos, so care must be taken be suitable attired and to use IVF certified disinfectants in the lab. A lot of priority must be given to proper documentation of all media, consumables, patient history, treatment, cryopreserved samples and any adverse events that occurred in the lab.

(xvii) Documentation : Impeccable documentation plays a vital role in the functioning of any responsible ART centre. Documentation involves recording of all possible patient details like medical history, previous treatments/complications if any; unique ID allocation and report filing; procedures undertaken and all relevant consents/declarations; media/disposables lot number and expiry dates for a retrospective analysis if required and treatment outcome and adverse occurrences if any.

Over the last 40 years IVF has transformed the treatment of infertility. Along with the complexities of the treatment, there have also been incidences of avoidable and unavoidable errors. The outcome of ART treatment has far reaching consequences and hence it is the responsibility of service providers to ensure minimal risks and errors at every step of the procedure. To summarise, one way to achieve this is by employing educated and skilled staff and ensure clear communication between all involved in the treatment; proper documentation and constant vigilance; timely quality checks, maintenance and service of equipments, continual internal and external audits and strict adherence to SOP's that should be revised time to time in accordance with emerging techniques and latest evidence. However, it is prudent to accept that some errors are inevitable. In case of an adverse event, it should be timely acknowledged and recorded. There must be a system of reporting these errors and sharing them with other ART providers that may act as a valuable learning tool and to develop a consensus on frequency of errors and a way to eradicate them. Keeping a track of non-conformances might enable us to prevent more serious ones for patients attempting ART treatments.

CLINICAL PATHWAY TO AVOID ERRORS DURING OPU/ ET

Ovum pick up for IVF

Pre-op : [one day before OPU]

1. Patient file is checked on the day of hCG or 1 day after that by consultant and front office before it is sent to the OT / IVF Lab.
2. Date, time of administration and trigger used [hCG or GnRh-a] confirmed.
3. Patient file is checked for

a. ALL relevant Consent Forms are filled and signed as per the check list

b. History sheet, allergies, stimulation protocols, drugs used are filled in detail
c. Any special attention needed by the patient e.g. cryopreserved semen to be used.
4. IVF laboratory informed about the procedure, time, any special needs.

On day of OPU Procedure

The anesthetist should examine the patient and confirm that the relevant consent forms are signed by all parties concerned.
The doctor/anesthetist or a nurse would assist the patient to the operation theatre.

1. Before the aspiration the nurse should:

a. Prepare the operation theatre table and trolley
b. Ensure that the required staff is present (doctor, anesthetist, nurse/helper, embryologist)
c. Patients name and unique identification number and husband's name should be verified/confirmed before draping and anesthesia.
d. Identity check : Ask the patient to speak out her name and communicate it to the IVF Lab.
e. Note down the procedure data in the OT book.

2. OocyteAspiration

(xviii) Before the procedure the test tubes for follicular fluid collection must be pre-warmed at 37°C.
(xix) A dry run to check the functioning of all equipment like aspiration pump is desirable before OPU.
(xx) The oocytes should not be exposed to follicular fluid for long, so the lab should be adjacent to the OT and oocyte identification must be done quickly after aspiration. Proper labeling of the petridish with double witnessing is mandatory.
(xxi) The husband should be provided with a sterile container for collection of fresh semen sample. His name and unique identification number should be written with a marker on the container. If it's a case of home collection of semen separate consent form should be filled and duly signed by both partners.

Post Operation Care

a. Proper notes should be completed on the number of mature follicles seen and number of oocytes retrieved
b. Double witnessing system with two embryologists should be followed during aspiration as well as post aspiration during fertilization of gametes.
c. Electronic witnessing system / RFID should be used if available during embryo culture .

GENERAL RULES FOR THE ASPIRATION PROCEDURE:

1. The operation theatre schedule is received a day before the procedure,
2. The OPU schedule is prepared and is intimated to the Embryologist to make the necessary preparations
3. There should be 2 copies, one inside the OT and the other one at the nursing station.
4. It is very important that the patient has signed the relevant Consent Forms; the negative serology tests results are within 6 months; the patient is fasting for 6-8 hours/ overnight ; hCG administration and its time should be verified
5. The preference is to use a fresh semen sample. In cases where a fresh sample is not possible e.g. if husband not in town; cryopreserved semen is kept as back up.
6. Before or after the OPU , the patient's partner is given a sterile container to provide semen sample.
7. If any alterations to the procedure are mandated it should always be with the permission of the senior Embryologist.
8. The nurse/doctor should always use the name and the last name along with unique identification number of the patient when the patient is entering the operation theatre and repeat it to the Embryologist
9. The OT register should contain the following information : the time of entry/exit of the pt, the type of surgery, doctor, anesthetist, nurse, type of anesthesia, blood pressure and heart rate
10. Prepare the discharge instructions, where the patient would verify her name and contact details for the IVF Laboratory.

Embryo Transfer(ET)

Previous day :

• Patient is informed about the time of reporting and need of a full bladder . If the ET is to be carried out under anesthesia , she is asked to come with 6 hours of fasting and to come with an attendant.
• ET list is prepared and shared with respective departments

On the EmbryoTransfer Day:

• Prior to the ET Procedure
1. Embryos are graded and selected for ET and cryopreservation by the clinician and the embryologist after discussion with the patient.
2. Before ET the nurse should:
a. Ensure that the required staff is present (doctor, anesthetist, nurse/helper, embryologist)
b. Identity check: Ask the patient to speak out her full name along with husband's name, verify it with that on the wrist band and communicate it to the IVF lab.
c. Follow the SOP step by step for embryo transfer.
d. Discharge the patient with all instructions from the clinician.
e. Provide the patient with contact details in case of emergency.

ISAR & FEQH

(Forum of Enhancement of Quality in Healthcare)

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What is Virtual/ e-Audit?

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- Physical Presence of auditor not required.
- Documents shared by E-mail/ Google Drive/ Box & verified on live video conferencing.

Why Accreditation With ISAR?

- Uniquely designed for IVF clinics.
- 3rd party audit (No ISAR member involved in audit)
- Based on ISO-Principles.
- Prepares you for future audits like ICMR.
- Provides you with standard SOPs & quality policy.
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Benefits of Virtual Accreditation

- Time & cost efficient.
- Ease of carrying the audit for remote locations.
- Saves the expenditure on audit logistics.
- The best audit team involved.

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North-East State Chapter Contribution

OBESITY & INFERTILITY

INTRODUCTION

"Obesity does not run in family; it happens because nobody runs in the family!!"
Obesity has emerged as a growing public health concern over the past four decades, owing to the lifestyle changes in the population, intake of energy dense food and lack of proper health care system. WHO defines Obesity and Overweight as abnormal or excessive fat accumulation that presents a risk to health. Modern studies have proven that obesity is not merely a result of laziness and lack of willpower but it is a multifactorial health problem. On one hand, it causes an increase in the risks of hypertension, diabetes mellitus, coronary artery disease and malignancies like breast, endometrial and colon cancers, while on the other hand, it significantly disrupts the reproductive performance in both male and female.

EPIDEMIOLOGY

About 13% of the world's population (11% of men and 15% of women) were obese in 2016. As per a study by ICMR INDIAB in 2015, India has a prevalence of obesity ranging from 11.8% to 31.3%.

OBESITY IN THE INDIAN SUBCONTINENT

Asian population, particularly Indians, have a greater amount visceral adipose tissue compared to Europeans and African population. Also they have a genetic tendency towards central obesity. Leptin, also known as the "Ob Gene", is a hormone located on chromosome 7 that balances food intake and energy expenditure. In experimental mice models, leptin has been found to cause obesity either due to signal disruption or receptor mutation. According to a study published in Nature Genetics in 2000, 22 different Single Nucleotide Polymorphisms (SNP) near to MC_4-R (Melanocortin 4 Receptor) gene were studied and scientists had identified an SNP named rs12970134 which was mostly associated with waist circumference because it caused permanent hunger in these people that led them to eat voraciously. This SNP was found to be highly prevalent in the group of 200 Indians in the study.

TYPES OF OBESITY

Obesity can be Central or Peripheral based on the fat distribution. In central obesity, fat gets accumulated in the abdomen and is more prone for morbidity, whereas in peripheral obesity, fat around the thighs and buttocks has a protective effect. Various studies suggest that aging, physical inactivity, sex hormones and excess intake of carbohydrates are determinants of visceral fat accumulation around abdominal organs.

EFFECT OF OBESITY ON FERTILITY

In females, obesity has been closely associated with Metabolic Syndrome, Insulin Resistance and Poly Cystic Ovarian Syndrome(PCOS) owing to neuroendocrine disturbances. Obesity causes increased peripheral aromatization of androgen to estrogen, while insulin resistance and hyperinsulinemia lead to hyperandrogenemia. This impairs the gonadotropin secretion. Also, it decreases other factors like Insulin-like Growth Factor Binding Proteins(IGFBP), Sex Hormone Binding Globulin(SHBG) and Growth Hormone(GH) but increases Leptin levels. Although less well documented, obesity in males impairs sperm concentration, motility, morphology and DNA fragmentation by disrupting the Hypothalamo-Pituitary-Gonadal axis through Testosterone and Oestrogen, and probably a reduced Sertoli cell function. Insulin resistance, hyperinsulinemia and hyperglycemia have shown to have a suppressive effect on sperm quantity and quality. Elevated temperatures within the scrotum , due to varicocele, using laptop on the lap, immersion in a sauna bath, etc. have deleterious effects like reduced sperm motility, increased oxidative stress and DNA fragmentation.

EFFECT OF OBESITY ON ASSISTED REPRODUCTIVE TREATMENT OUTCOME

Obese women respond poorly to ovulation induction, require higher doses of gonadotropins, longer duration for follicular development and yield less oocytes. It also leads to lower embryo quality, reduced pregnancy and live-birth rates and higher rates of miscarriages. Obesity, per se, may cause technical difficulties like ultrasound visualisation of the ovaries and oocyte retrieval. Whereas few studies suggest a poor endometrial receptivity in obese women, other studies blame the quality and yield of oocytes for higher rates of cycle cancellation. Raised BMI in men is associated with lower fertilization rates, poor quality embryos and reduced clinical pregnancy rates in IVF/ICSI cycles.

HOW TO MEASURE OBESITY?

The various ways to measure obesity include – field methods like Body Mass Index (BMI), Waist circumference, Waist-to-hip ratio, Skin Fold Thickness, Bioelectrical Impendence, and more sophisticated methods like Dual Energy X-ray absorptiometry, Underwater weighing (densitometry), Air Displacement Plethysmography, Dilution method (Hydrometry), Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI).

Body Mass Index (BMI), previously termed as the Quetelet Index is calculated by dividing a person's weight (in kilograms) by the square of the height (in metres).

Table 1 :- WHO classification of BMI.

BMI (kg/m^2)	CLASSIFICATION
< 18.5	Underweight
18.5-24.9	Normal weight
25-29.9	Overweight
= 30	Obesity

These values were also adopted by the National Heart, Lung and Blood Institute (NHLBI), NIH, North American Association for the Study of Obesity and published in their practical guide in the year 2000. In a consensus meeting in New Delhi in November 2008, as well as in Asia-Pacific Recommendations on "How to define Obesity?" in 2008, the cut-off for BMI for Asian population was set at a lower limit to include more number of people in the high risk group.

Table 2 :- Asia-Pacific Classification of BMI.

BMI (kg/m^2)	CLASSIFICATION
< 18.5	Underweight
18.5-22.9	Normal weight
23-24.9	Overweight
= 25	Obesity

Limitations of BMI include failure to distinguish between body fat and lean body mass and it does not predict body fat in the elderly as it is in younger and middle aged people. On the other hand, CT scan and MRI are considered to be the most accurate as they allow for measurement of fat of specific body compartments. However, disadvantages are high expense and limited mobility of the instruments and contraindication of CT Scan in pregnancy.

WHY AND HOW TO TACKLE OBESITY?

Weight loss of 5-10% significantly improves endocrine parameters and hence, improves the reproductive outcome[10]. Various options to tackle the problem include lifestyle intervention (Diet, Exercise, Behaviour therapy), Pharmacotherapy and Surgery.

I. Lifestyle Intervention

a) Diet

The Obesity Guidelines recommends an energy deficit of 500-750 kcal/d that leads to an average weight loss of 0.5-0.75 kg/week[11] . Daily energy requirement can be calculated by the Harris-Benedict equation, the WHO equation[13] or the American Gastroenterological Association Dietary Guidelines.

Table 3 :- The four types of dietary regimens are as follows–

Diet	Daily Calorie Composition	Mean weight loss	Advantages	Disadvantages
Low Calorie	800-1500 kcal 55-60% carbohydrate <30% fat	~10% in 3-12 months.	Reduction in Blood Glucose, Serum lipids and Blood Pressure.	Difficult compliance in the long run.
Low Fat	1000-1500 kcal 20-25% fat	~5% in 2-12 months.	Reduction in Blood Glucose, Blood Lipids and Blood Pressure.	Less Palatable. Increases triglycerides.
Low and very low Carbohydrate	1000-1500 kcal 60-150g (low carbohydrate)	~5% in 2-12 months.	Faster initial weight loss than low fat diets. Reduces Blood Glucose, Blood	Ketosis when carbohydrate intake <50g/day.

b) Physical Activity and Exercise

The American College of Sports Medicine (2009) recommended that exercise of moderate intensity for 150-250 min per week helps to prevent obesity. For maintenance of weight after a significant reduction, atleast 200-300 min per week moderate intensity aerobic exercise is required. Exercise increases satiating efficiency of a fixed meal and thereby reduces the food intake.

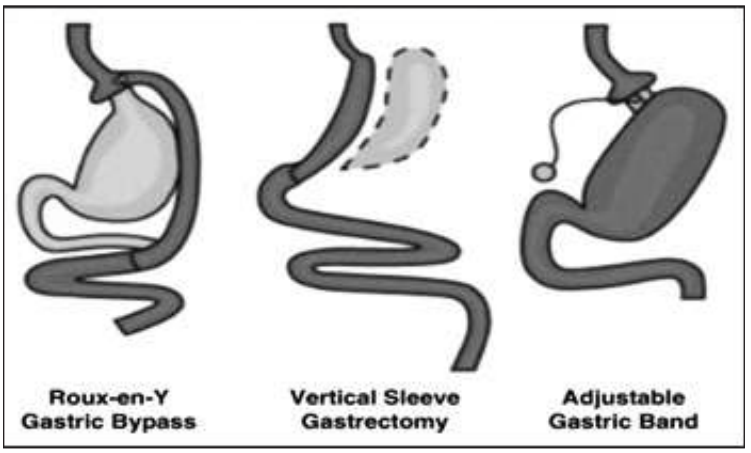
c) Behaviour Therapy

It involves strategies to modify the eating habits and physical activity like weekly goal setting, problem solving, cognitive restructuring and coping with dietary lapses.

II. Pharmacotherapy-Pharmacotherapy has been recommended for patients who cannot achieve adequate weight reduction with only lifestyle modification. It helps the patients to adhere to dietary recommendations by increasing satiety or by reducing hunger. It also counteracts the hormonal alterations caused by weight loss and calorie restriction. Various drugs that may be used include – Orlistat, Cetilistat, Sibutramine, Lorcaserin, Phentermine/Topiramate, Naltrexone/Bupropion, Liraglutide. In a consensus meeting of ESHRE/ASRM in 2007, Orlistat and Sibutramine have shown a weight-loss independent effect on androgens and insulin resistance. Orlistat is a gastrointestinal lipase inhibitor that causes 2.9-3.4% weight loss of the initial body weight. However it has side effects like steatorrhoea, flatulence, fecal incontinence and increased defeacation. Although FDA approved, it was banned in 2010 due to reports of hypertension and heart problems. Cetilistat is a new drug that works in similar fashion like Orlistat. Sibutramine is an appetite suppressant that was banned due to its association with vascular accidents.

III. Bariatric Surgery-According to United States National Institute of Health (NIH) 2013 guidelines, bariatric surgery is recommended for patients with BMI ≥40 kg/m2 without comorbidities or ≥35 kg/m2 with comorbidities who fail to respond to non surgical methods. A recent Asian Concensus Meeting on Metabolic Syndrome recommended that surgery can be considered for Asian adults with BMI ≥30 kg/m2 with central obesity and atleast two features of metabolic syndrome. Surgery can be reversible restrictive or irreversible malabsorptive. The most commonly used procedures include Roux-en-Y gastric bypass, Gastric banding and sleeve gastrectomy and less frequent procedure like biliopancreatic diversion. Roux-en-Y gastric bypass is the gold standard, it produces a median weight loss of 31.5% of initial weight at 3 years.

Figure 1: Types of commonly performed Bariatric Surgeries



FERTILITY AND PREGNANCY AFTER BARIATRIC SURGERY

Various studies have shown improvements in sex hormone profile, improvement in luteal function and a shortening of follicular phase length that led to regular menses after bariatric surgery. The improvement in fertility is irrespective of the type of bariatric surgery performed but is related to the amount of weight lost and the pre-conceptional BMI achieved. As per guidelines, all women of reproductive age undergoing bariatric surgery should be advised contraception and pre-conceptional counseling alongwith life-long nutrient supplementation . As per the American College of Obstetrics and Gynaecology (ACOG) and the European Association for the Study of Obesity, the first post-surgical year is a catabolic time frame, when pregnancy may compromise fetal nutritional supply. Hence, postoperatively , contraception for 1 to 1.5 years is needed alongwith ultrasound monitoring for fetal growth.

CONCLUSION

The detrimental effects of obesity on different systems are being studied extensively. Irrespective of the gender, obesity compromises the reproductive performance in natural as well as assisted conception. The main pathology behind obesity, i.e. visceral fat, is best assessed by imaging. Treatment strategy involves lifestyle modification, pharmacotherapy and surgery. After bariatric surgery, adequate contraception and pre-conceptional counselling is sine-qua-non. Newer obstetric challenges may pave the path to specific recommendations pertaining to reproductive health management after bariatric surgery.

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Haryana State Chapter Contribution

CORRELATION OF THYROID AND PROLACTIN WITH INFERTILITY

INTRODUCTION

Hyperprolactinemia is defined as presence of abnormally high level of prolactin in the blood. Its prevalence varies from less than 1-17 % in women of reproductive disorders. Polactin is secreted in pulsatile manner following a circadian rhythm with highest concentration during sleep and lowest in morning about 2-3 hours after waking up. It has 3 molecules,

1. Monomeric or little PRL (molecular weight 22500),
2. Big PRL(molecular weight 50000) and
3 Big Big PRL, macroprolactin- (molecular weight > 100000)

This Polymorphism explains discrepancy between immunoassays and biological effects. Macroproactin is biologically inactive but detected by the same radioimmunoassay as the biologically active prolactin.

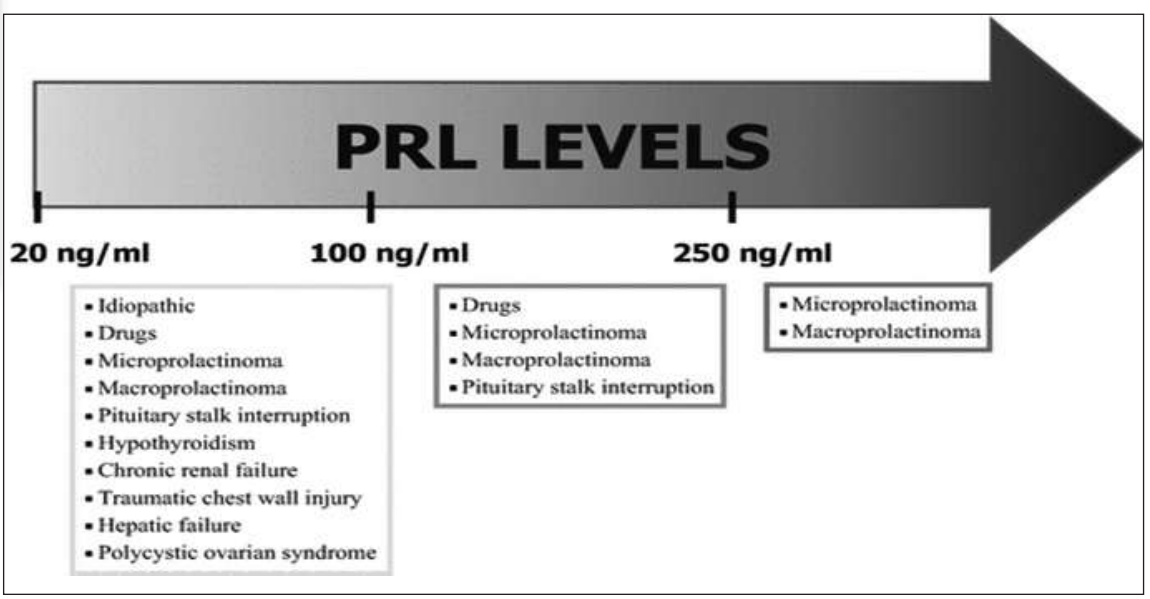
Normal Prolactin levels in both sexes is 5-20 ng/ml. Ideally, a person's blood sample should be drawn 3 to 4 hours after waking. Current best practice recommends that sera with elevated prolactin are subfractionated using polyethylene glycol (PEG) precipitation to provide an indication for whether or not macroprolactin is present. According to WHO standards PRL level more than 250ng/ml indicate prolactinoma and PRL more than 500ng/ml is considered diagnostic for macroprolactinoma. Prolactinomas less than 10 mm in diameter are termed Microadenomas and more than 10 mm are Macroadenomas.

CAUSES OF HYPERPROLACTINEMIA

- Physiological – pregnancy, lactation
- Idiopathetic – 30-40% of cases
- Prolactinoma – 25-30% of the cases
- Primary hypothyroidism
- Medications – Drugs Cusing interruption of dopamine synthesis
- PCOS patients
- Stress

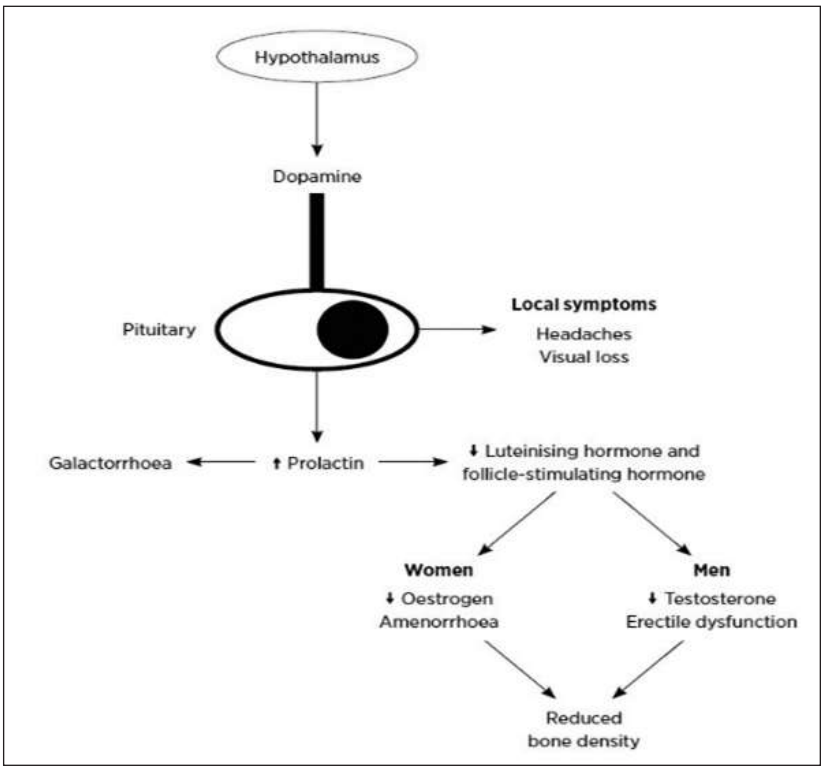
CLINICAL PRESENTATION:

In patients with hyperprolactinemia suppression of pulsatile GnRH is there which results in hypogonadotrophic hypogonadism. It causes delayed puberty, hypogonadotrophic hypogonadism, primary or secondary amenorrhea. Women of reproductive age present with menstrual irregularities



in the form of oligomenorrhea, amenorrhea, galactorrhrea, decreased libido, infertility, decreased bone mass. Prolonged hypoestrogenism results in osteopenia (25%). Women may also present with signs of chronic hyperandrogenism, such as hirsutism, acne due to increased DHEAS secretion from adrenals. Patients with prolactinomas present with additional pressure symptoms, headache visual field defects and abnormal pituitary functions.

Men may have Erectile Dysfunction, Decreased Libido, Infertility, Gynecomastia, Decreased bone mass, reduced muscle mass and osteopenia.



MANAGEMENT: (See Figure)

Prolactinomas are suspected with prolactin levels more than 250 ng/ml and MRI with gadolinium enhancement is recommended.

1. Idiopathic hyperprolactinemia:

DRUG	CABERGOLIN	BROMOCRIPTINE
Dose	0.25-0.5mgtwice weekly	1.25-2.5mg/day
Maintenance	0.5-1 mg/ week	5-7.5mg/day
Advantage	Selective Dopamine receptor type II agonist, fewer side effects, greater potancy	Less or No risk of Hypertrophic Valvular heart disease on long term use
Disadvantages	Risk of Hypertrophic Valvular heart disease on long term use	Non selective agonist with less potancy

2. Microadenoma with Hyperprolactinemia: Dopamine agonist are first choice treatment as they effectively lower prolactin levels and decreased size by more than 90%. Patient intolerant or failed to respond to one drug do well with other drug. Therapy can be discontinued with normal serum prolactin levels and very little or no visible residual tumor on MRI.

3. Macroadenoma with Hyperprolactinemia: Dopamine agonists are the first line of treatment with surgery and radiotherapy reserved for drug intolerant patients, resistant patients, or very large macroadenoma (> 3 cm), where transnasal, transsphenoidal microsurgical excision is done. Recurrence may be seen in macroadenoma patients within 5 years post-surgery.

4. Others causes of Hyperprolactinemia: Correction of hypothyroidism, associated medical disorder, stoppage or replacement of culprit drug.

Management during pregnancy: Approximately 80% of patients will achieve pregnancy with dopamine agonist. Risk of enlargement is 1-2% with microadenomas and 15-20% in macroadenomas. Treatment may be safely discontinued when pregnancy is established in absence of symptoms regardless of size of adenoma. Bromocryptin is safe during pregnancy.

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Materna HCG® 5000 IU 10,000 IU

Materna® rFSH 75 IU 150 IU

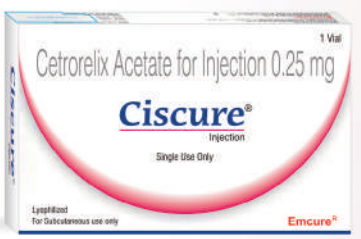
Materna® Depot 3.75 mg

Materna® LMD

Leuprolide Acetate For Injection 4mg / 4ml

Ciscure®

Cetrorelix Acetate for Injection 0.25 mg



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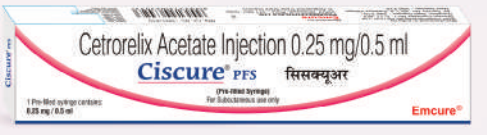

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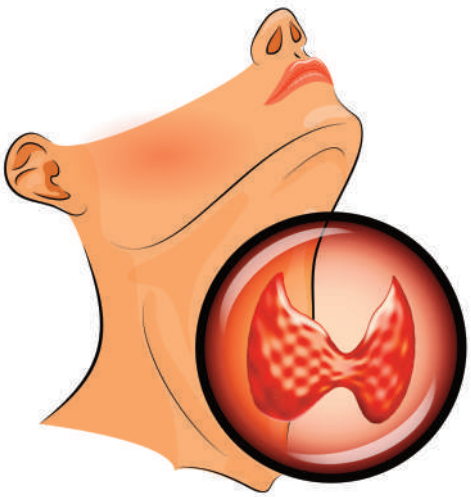


THYROID DISORDERS AND INFERTILITY

Introduction

Thyroid disorder is the second most common endocrine condition in women of childbearing age. Women between 18-35yrs are mostly affected by thyroid abnormalities. Inadequate treatment of overt hypothyroidism or subclinical hypothyroidism (SCH) can lead to infertility, miscarriage, adverse obstetrical and neuro developmental outcomes. Thyroid hormones are involved in control of menstrual cycle and fertility affecting the actions of follicle-stimulating hormone and luteinizing hormone on steroid biosynthesis by specific triiodothyronine sites on oocytes. Common thyroid disorders are overt hypothyroidism / hyperthyroidism, subclinical hypothyroidism / hyperthyroidism and autoantibodies positivity.

Hypothyroidism

Prevalence is 2–4% in women of reproductive age group. It can cause anovulation, luteal phase defects, hyperprolactinemia and sex hormone imbalance. Current recommendations include preconception TSH value to ≤2.5 mIU/L. Overt hypothyroidism is TSH >10Miu/L with below normal free T4 levels.

Subclinical hypothyroidism (SCH)

Mild form of hypothyroidism defined as elevated TSH with normal free thyroxine levels. Recommended upper limit is 4.0 mIU/L. Hypothyroidism stimulates TRH release from hypothalamus increasing release of TSH and Prolactin. Increased level of serum prolactin has been reported in 30% of patients with primary hypothyroidism.

Clinical manifestations

- Menstrual irregularities
- Anovulation
- Luteal phase defect
- Impaired embryo quality
- Interference with the release of egg on time
- Increased risk of miscarriage
- Adverse pregnancy outcomes
- Adverse neonatal outcomes

TSH levels should be below 2.5Miu/l in overt as well as subclinical hypothyroidism. These patients should be supplemented with levothyroxine. Test has to repeated after 6 weeks. Anti TPO antibodies should be measured when TSH level is elevated (generally above 4 mIU/L) and free Thyroxine (T4) level is low (under 0.8 ng/dL). Maintaining levels of TSH below 2.5 mIU/l has shown improvement in implantation rates and clinical pregnancy rate. A study done to assess thyroid function and embryo quality found that women with high normal TSH levels or high TSH levels had impaired embryo quality. Also if there were Anti-TPO antibodies, embryo quality was poor. Hypothyroidism in males causes loss of libido, testicular dysfunction and deranged semen parameters.

Hyperthyroidism

Prevalence of subclinical hyperthyroidism is seen in 1.5%. Chief effect of hyperthyroidism on fertility remains ill defined. Menstrual irregularities are seen in 65% of them. Though these women usually continue to ovulate, they have increased levels of serum sex hormone binding globulin, increased gonadotropin response to GnRH. Antibodies associated with Grave's disease are known to have more impact on the fetus and cause neonatal thyrotoxicosis or miscarriage.

Euthyroid thyroid auto antibody positive women

Auto immune thyroid disease is the most common cause of hypothyroidism in women of reproductive age affecting 5-10% . These are found mainly with Hashimoto's thyroiditis. There prevalence has been found to be consistently higher in infertile population especially PCO women and increased estrogen/progesterone ratio is characterstic. Also it has been postulated that these antibodies may interfere with the fertilizing capacity of metaphase 2 oocytes.

Treatment:

Directed towards cause, which could be Grave's disease, multi nodular goitre or solitary thyroid nodule. Anti- thyroid drugs are commonly used to treat thyrotoxicosis associated with Grave's disease. Alternatively, radio-active iodine treatment is advocated and it is not shown to affect gonadal function in lower doses as required in Grave's disease. Guidelines suggest women to delay pregnancy for 6 months to attain target TSH values on T4 replacement therapy.

Hypothyroidism is very rare in males with occurrence of only 0.1%. In case of prolonged pre pubertal hypothyroidism due to drop in LH, FSH levels the leydig and sertoli cells are less stimulate to differentiate into mature cells also increased testicular size is observed along with a significant drop in mature germ cells. In higher doses radio-active iodine, as for thyroid cancer ablation, may cause azoospermia and hence sperm cryopreservation is important.

docplexus

PREVALENCE, SYMPTOMS AND DIAGNOSIS OF THYROID

PREVALENCE

Nearly **1** in **20** people has some kind of thyroid disorder.

Women are more susceptible to have thyroid than men.

CHANGE IN LEVELS OF THYROID CAUSES

TSH

High TSH- Hypothyroidism

Symptoms

- Tiredness
- Weight Gain
- Depression

Low TSH- Hyperthyroidism

Symptoms

- Weight Loss
- Anxiety
- Sore Eyes
- Excessive sweating

THYROID DISORDERS

- Goiter
- Thyroid Cancer
- Thyroid Nodules
- Iodine Deficiency
- Infertility
- Irregular menstruation

PHYSICAL EXAMINATION

- Dry skin
- Swelling under eyes
- Slower reflex

DIAGNOSTIC TESTS

- Blood Test: T3 and T4 test, TSH levels
- Iodine Uptake Test

Dr. Kedar Padte
Chairperson

Dr. Abhijit Kamat
Secretary

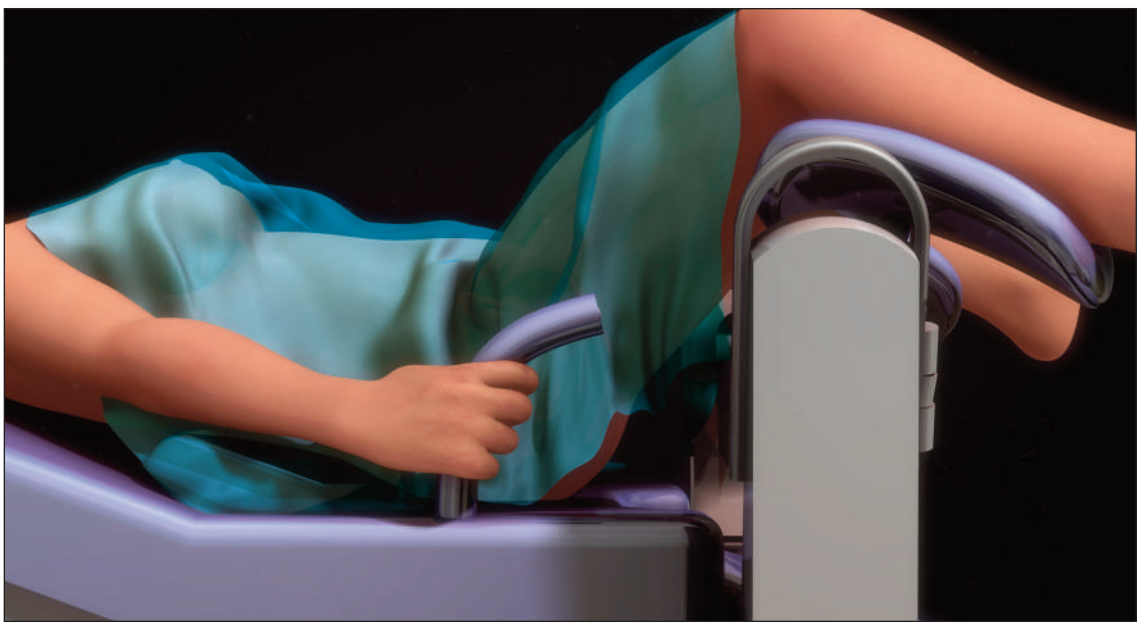
Dr. Vikram Dukle
Treasurer

Dr. Sachin Narvekar
Member

Goa State Chapter Contribution

EMBRYO TRANSFER

OPTIMIZING OUTCOMES



INTRODUCTION

The birth of Louise Joy Brown (born 25 July 1978) started off a revolution called in-vitro fertilization which has benefited countless infertile couples since then. Though IVF cycles proceed up to the stage of embryo transfer (ET) in more than 80 % cases, only a small number of them result in live birth. Traditionally, little attention has been focused on the technique of embryo transfer. It is often viewed as an unimportant variable in the success of an IVF cycle, and clinicians are often reluctant to change their habits or methods in performing embryo transfer. Many factors have been proposed to explain the disparity between embryonic development and pregnancy rates (PR). Genetic abnormalities of embryos and defects in uterine receptivity have been implicated. However, much of the inefficiency of embryo implantation may stem from embryo transfer technique. Uterine contractions, expulsion of embryos, blood or mucus on the catheter tip, bacterial contamination of the catheter, and retained embryos have all been associated with problematic and unsuccessful embryo transfers.

Most authors have reported a significant reduction in clinical pregnancy rate with 'difficult' embryo transfers. Endometrial trauma may occur even in transfers perceived to be 'easy' and is difficult to identify in the absence of obvious bleeding. Hence, it is prudent to follow meticulous steps to ensure superior outcomes. Let us discuss some of the factors which we need to consider.

DAY OF TRANSFER

It is believed that delayed transfer of embryos after IVF allows for a better selection of good quality embryos. There is no significant difference in pregnancy and implantation rates between day 2 and day 3 transfers when fertilization was by ICSI. When fertilization is by IVF a statistically higher implantation rate is found in the day 2 versus day 3 ET. The higher implantation rates seen with blastocyst transfer makes the choice to transfer only two embryos easy. Selection of embryos for transfer is also easier for the embryologist, as is the decision of which surplus embryos to cryopreserve. Because of the larger diameter of blastocysts, the

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rate of ectopic pregnancy may be decreased after blastocyst transfer. Uterine receptivity may be enhanced for day 5 or blastocyst transfers.

In vitrified transfer cycles, day 7 blastocysts were associated with adverse perinatal outcome regarding higher risk of low birth weight compared with day 3 cleavage-stage embryo, while blastocysts with diverse growth rates embrace similar developmental viability regardless of blastocysts vitrified on day 5, day 6, or day 7.

ULTRASOUND GUIDANCE

Ultrasound guidance facilitates placement of soft catheters; avoids touching the fundus; confirms that the catheter is beyond the internal os in cases of an elongated cervical canal; and allows proper direction for the catheter. Thus, it is expected to minimize endometrial trauma and 'difficult' transfers. It also rules out endometrial fluid at the time of ET.

Ultrasound guided ET has been consistently associated with increased number of 'easy' transfers and higher pregnancy rates. It's a matter of debate whether ultrasound helps in those cases where uterocervical length has already been measured earlier and/or a mock trial has been done. However, selected ultrasound guidance for an anticipated difficult embryo transfer is not recommended especially since the difference in bladder filling at the time of mock and actual ET may result in an unexpected difficult transfer.

ENDOMETRIAL THICKNESS

A recent systematic review and meta-analysis (Kasius et al., 2014) concluded that the EMT, assessed on the day of triggering final oocyte maturation, has a limited capacity to identify women who have a low chance to conceive after IVF, while acknowledging that below a cut-off of 7 mm, a lower chance of pregnancy can be observed . However, it is unclear whether the EMT is more an epiphenomenon of potentially multiple predictive factors for IVF success, such as ovarian response, age and patient history. While a few studies quoted extremely poor results for EMT above 12 or 14 mm, others have reported a directly proportional increase in pregnancy rate, with no such threshold limit. Interventions aimed at increasing the EMT such as sildenafil, aspirin or heparin have not been found to influence the PR.

TRIAL EMBRYO TRANSFER

Performing a mock ET before the IVF cycle is associated with significantly higher PR. Performing a mock transfer helps to measure the length of endometrial cavity, its direction, the amount of bladder filling required. It also rules out cervical stenosis and sometimes coexisting pathology like endocervical polyps which cause bleeding. While, a mock ET on the day of oocyte retrieval is not associated with a reduced PR, doing it in the previous cycle allows one to perform cervical dilatation prior to starting IVF cycle in case stenosis is discovered. Cervical dilatation on the day of OPU or ET of a fresh transfer cycle, is associated with a poor PR.

TYPES OF CATHETER

Soft malleable catheters have been associated with better outcomes compared to firm or hard catheters. It is imperative to note that soft catheters usually have a firm outer sheath to guide them in the correct direction. Crossing the internal os with this outer sheath could possibly cause the release of prostaglandins and uterine contractions, thus negating any benefit of soft catheters. Therefore, the outer sheath should be stopped short of the internal os, and only the inner catheter advanced into the uterine cavity.

CATHETER POSITION

The majority of the studies have found that embryo placement impacts pregnancy rates, with pregnancy rates highest when the embryo was placed in the upper or middle area of the uterine cavity, at least 1 cm away from the fundus. No difference is noted when the catheter tip was 2 cm from the fundus or in the middle third of the uterine cavity, indicating that both are acceptable options.

The position of the air bubbles after embryo transf er is related to pregnancy rate; the highest pregnancy rates are found when the air bubbles end up closer to the fundus.

TIME TAKEN FOR TRANSFER

Although previous studies have suggested that a time cut off of 120 seconds or even 60 seconds leads to worsened clinical outcomes, recent studies have not bee able to prove a significant difference in PR when loading-transfer time was even up to 3 minutes. This suggests that there is no specific cut off duration for embryo transfer, rather other factors to optimize embryo transfer should be stressed upon.

TECHNIQUE OF TRANSFER

Removing cervical mucus before ET and immediate withdrawal of catheter following ET were associated with increased PR.

The factors that did not influence the pregnancy rate were: (1) analgesics (2) prophylactic antibiotic (3) anaesthesia (4) bed rest after ET. The speed of injection and retained embryos with immediate retransfer also did not affect the outcome.

Embryology Section

SELECTING THE BEST INCUBATORS

THE HEART OF EMBRYO CULTURE SYSTEMS

Charudutt Joshi
Clinical Embryologist

Krishna Chaitanya
Member

Incubators in the IVF laboratory play a pivotal role in providing a stable and appropriate culture environment required for optimizing embryo development and clinical outcomes. With technological advances, several types of incubators are now available and careful consideration is required for selection.

Examination of variables, such as recovery/stabilization of temperature, gas atmosphere and humidity, as well as understanding various approaches utilized by each device to regulate these variables, is critical. Other factors, both technical and practical, must also be considered when selecting an incubator. Importantly, proper management, depending upon the patient volume and workflow, is vital in optimizing function of any incubator, regardless of the technology incorporated.

This review highlights incubator function and reviews key environmental variables controlled and the technology utilized in various units.

Minimizing environmentally induced stress within the IVF laboratory is crucial in creating a culture system optimized for embryo development and to achieve maximal assisted reproductive outcomes.

Key environmental variables to consider within the culture system include pH of the culture medium, temperature, media osmolality and air quality. Importantly, all of these potential stressors can be impacted by the laboratory incubator. As a result, the incubator is arguably the most important piece of equipment in the laboratory, controlling multiple environmental variables and housing the embryos for the vast majority of their time in vitro. Thus, incubator selection and management is critical to ensure success of an IVF programme.

With advances in technology, multiple incubator types with varying capabilities and different methods of regulating their internal environment. As a result, selection of an appropriate culture incubator for the IVF laboratory has become a complex process. This review deals with few functional aspects of incubators to be considered which would guide in smart investment for optimal outcomes.

KEY ENVIRONMENTAL VARIABLES

pH of the culture medium

The pH is defined as the negative $\log_{10}$ of the hydrogen ion concentration.

$$pH = -\log[H+]$$

Low pH number means the solution is acidic as it contains relatively higher concentration of hydrogen ions while the alkaline solutions exhibit high pH values and have lower hydrogen ion concentrations. A well-defined buffer system optimized to work in CO_2 rich environment is added in almost all cell culture media to maintain the pH. Usually, bicarbonate is used for this purpose. In the influence of CO_2, an equilibrium between carbonic acid and bicarbonate ion keeps the pH of the medium stabilized in the incubator at a specific temperature. Altitude and protein are also important factors. The partial pressure of CO_2 decreases at higher altitude causing reduced actual concentration of CO_2 in the incubator for the same setting. *Therefore, incubator needs to be set at higher % CO_2 to achieve the same pH of the medium at places located at higher elevation.*

Any culture media needs to be equilibrated before use. The time required for equilibration depends upon the volume of media, the surface area exposed, the oil overlay, and the type of culture.

Importance of pH measurement: pH of the culture medium is an important variable that can significantly impact gamete function and embryo development. Different culture media have different compositions. The manufacturers optimize their media according to their formulation and their intended use. Therefore, they provide the instructions for the use of specific media in specific conditions to achieve desired conditions. The recommended settings are %CO_2, temp ^oC and % relative humidity. Traditionally, the CO_2 analysers have been used to calibrate the incubator settings. However, it is realized that CO_2 measurement is only a surrogate marker & does not provide the correct information about the pH in the medium. The disparity between the actual values of CO_2 and Temperature inside incubator and the values

shown by the incubator's display is not uncommon. This disparity leads to suboptimal culture conditions.
Optimal pH: Optimal pH for growing the best embryo is not known with certainty. *However, what is known is that pH controls various intracellular processes required for embryo development. For example, if pH is lowered to 6.8 or increase more than 7.4 it affects the development of actin microfilament and positioning of the mitochondria. Sometimes, this damage is irreversible and leads to the poor-quality embryo.*
Studies have shown that different stages of embryo development have different nutritional requirement and different pH for proper metabolism which is practically impossible to attain. Therefore, the commercial media are designed to perform at range of pH between 7.2 and 7.4.

2-TEMPERATURE
Another primary function of the laboratory IVF incubator is to maintain an appropriate temperature for gamete function and embryo development. It is also well known that temperature can impact various aspects of gamete and embryo function, most notably meiotic spindle stability and possibly embryo metabolism. Temperature is also an important factor that can affect the pH of some media hence close monitoring of temperature fluctuations also required.

3- AIR QUALITY
An additional variable related to gas atmosphere that impacts culture conditions is air quality. Air quality, specially presence and amounts of volatile organic compounds (VOC), may compromise embryo development, although the relevant concentrations of VOC are still unknown. As a result, most laboratories have dedicated air handling systems to filter out particulates as well as VOCs and various studies indicate a benefit to embryo development and/or outcomes once air quality is improved. However, while outside air quality may be important, it is the quality of the atmosphere inside the incubator that is likely of more concern.
VOCs have been detected in gas supply tanks used for IVF incubators. In these cases, filtering the supply gases through inline filters prior to incubator entry may be an effective approach to improve incubator atmosphere. These inline filters are fitted with the HEPA filter and activated charcoal and/or potassium permanganate that reduce particles and VOCs from the gas supplied to the incubator. An emerging approach to improve air quality to some incubators includes recirculating atmospheric air past a UV light source for photocatalytic breakdown of VOCs.

HUMIDITY & MEDIA OSMOLALITY :
Many incubators regulate humidity to avoid media evaporation during culture to avoid harmful rises in medium osmolality that can compromise embryo development. This humidification is usually achieved by placing a water reservoir in the bottom of box incubator chambers. In some benchtop incubators, the incoming gas is passed through a small water jar while others offer a dry incubation chamber without humidity.
Dry incubators make oil overlay mandatory.

Main components of any incubator
1} Heating system with insulation to maintain the temperature
2} Gas sensors to maintain required set points
3} Humidity control
4} Sterilization and maintenance.

Heating systems: By now we know the importance of temperature maintenance in a culture system. It is a critical parameter in selecting an incubator. We have two systems that are presently used.
A} Water Jacketed systems: Traditional incubators have a water jacket around the culture chamber. The jacket is filled with water and then heated to attain the desired temperature in the inner chamber. These water jackets prevent rapid fall in temperatures in case of long power outage but they also take long to heat up again. Condensation and maintenance problems are common with them
B} Air Jacketed systems: Advanced heating system. More accurate in maintaining temperature. In place of water, it is the air that is heated. The biggest advantage is maintenance and easy operation but it has a direct effect of environmental temperature and condensation.
C} Direct heating systems: They are fast, accurate, and reliable and there is no problem of condensation. Forced air circulation for maintaining temperature is its disadvantage.

Gas sensors: Most of the incubators are fitted with CO2 sensors alone or CO_2 and O_2 sensors both.
CO_2Sensors-
A} Thermal conductivity (TC} sensors: Thermal conductivity sensors function through measurement of resistance between two thermistors, with one enclosed and the other exposed to the incubator chamber. The presence of CO2 in the incubator chamber changes the resistance between the two thermistors and permits elucidation of gas concentrations. Importantly, the resistance, and therefore CO2 readings, of incubators using TC sensors are impacted by temperature and humidity Changes in temperature and relative humidity can affect the accuracy of the sensor.
Incubators using TC CO2 sensors tend to take longer to stabilize gas atmosphere following door opening. CO2 concentrations cannot be fully determined and subsequently adjusted until both temperature and humidity stabilize.
B} Infrared (IR) sensors: The sensor detects a reduction in the IR radiation from the emitter as the CO2 in the air

sample absorbs the IR, The amount of IR absorbed is relative to the levels of CO_2 in the air sample. IR sensors are largely humidity and temperature independent. Therefore, incubators regain the set CO_2 levels faster after door openings.
Incubators outfitted with IR sensors have become the preferred option in cell culture laboratories.
Oxygen sensors: Galvanic fuel cell sensor and Zirconium sensors used to measure O_2 concentration. The mechanism involves the emission of ions through electrodes. Zirconium sensors seem to be efficient sensors over galvanic sensors.
Some incubators use premixed gas with fixed concentrations. However, proper quality control is required to ensure that the premixed gas concentrations/ratios within the supply cylinder yield the desired pH of medium and growth conditions. Premixed gas may be supplied with a formal certificate of analyses by the vendor still, it needs to be verified through routine pH testing, independent gas measurement
Humidity control: In most of the box type incubators a water filled pan/tray is placed in the bottom section of the chamber. The water vapours keep the chamber humidified. In some benchtop/top loading incubators, the gas is bubbled through a water bottle before it is injected into the culture chamber. Some other incubators are "dry" incubators.

Sterilization and maintenance: Various methods have been proposed for cleaning and sterilization. It should be easy to perform and user friendly. It includes Wet sterilization (Heating the entire unit at 90 degrees for 12 hours), Hot sterilization (Heating the entire unit at 180 degrees for 30 minutes).
Commercially available non-embryo toxic disinfectants are used to clean and disinfect the incubators in IVF laboratories.

Gas monitoring and recovery
A critically important function of the laboratory incubator is to reliably provide an appropriate gas atmosphere. Specifically, regulation of CO_2 concentration is of paramount importance, as this gas helps regulate pH of the culture medium.
Additionally, reduced O_2 con- centration in the culture environment has, for many years, repeatedly been found beneficial for both animal and human embryo development and outcomes, most notably when used throughout the entire culture period to the blastocyst stage. Thus, modern IVF incubators should monitor and regulate both CO_2 and O_2 concentrations.
Independent of gas sensor or gas supply type, incubator volume also influences gas equilibration and recovery timing. Following door opening, traditional 'large-box' incubators (150–200 l) may require an extended time to refill with CO_2 and/or nitrogen gases. Thus, 'small-box' incubators (14–48 l) have come into use and, depending on workflow, may help improve gas recovery, reduce environmental stress and improve embryo development compared with larger incubators. More recently, benchtop/top load units of varying sizes/configurations designed specifically for clinical IVF have extremely small chambers (0.31–0.5 l), further improving gas atmosphere recovery time.

OTHER CONSIDERATIONS
Other considerations for incubator selection include approaches available for cleaning and sterilization reduce chances of contamination. Various incubators are constructed with copper containing alloys, as copper can act as antimicrobial and antifungal agent.
Quality control may be another variable to consider when selecting a laboratory incubator. Several optional features may be available on units that an assist with routine monitoring, including data logging capabilities to monitor real-time temperature fluctuations or number of door openings. Some incubator designs may make other aspects of quality control more difficult, although perceived limitations can often be overcome. For example, in bench- top/top load incubators, it may be difficult to measure pH of the culture medium. However, specialized pH meters or blood gas analysers can be purchased in some cases, or pH can be tested directly from the gas supply if using a cylinder of premixed gas. Alternatively, small test tubes can often be laid inside units to permit medium equilibration for subsequent measurement.
Finally, additional consideration must be given to cost and capacity of each incubator, as well as space occupied. Several incubators are required in any IVF laboratory to help avoid overcrowding and promote proper incubator management, as well as provide backup capabilities in case of unit malfunction or scheduled downtime for routine maintenance.

INCUBATOR MANAGEMENT
Following critical review of existing comparative studies, it becomes apparent that it is impossible to determine the 'best' incubator. This will vary from laboratory to laboratory based on specific use and needs.

Proper incubator management includes various approaches aimed at maintaining environmental stability inside the unit.

1) Distribution of patient samples and proper workflow to avoid overuse of any particular incubator. Overuse of an incubator results in the inability to maintain a stable culture environment due to repeated opening/closing.

2) An adequate number of incubators based not only on total cycle volume, but also on the time frame of when these cycles are performed. For example, an IVF laboratory that performs 200 cycles spread over the entire year will have a different incubator requirement than an IVF laboratory that performs the same 200 cycles in four batches a year because the workload for a single incubator will be greater for the laboratory that batches. The number of incubators required can be determined through analysing a particular laboratory's workflow, taking into account how many patients can fit into an individual unit (i.e. one patient per shelf or two patients per unit), how many patients will be seen within a period of time (i.e. 6 d) and other relevant variables.

3) Workflow between incubators must also be considered. Preferred use of a single incubator over others due to a convenient location can compromise the environmental stability of the individual incubator due to increased opening/ closing. It was demonstrated that reducing door opening from six to four times over a 6-d period on a small-box incubator utilizing a water jacket with TC CO_2 and galvanic O_2 sensors resulted in significantly improved human blastocyst formation (53% versus 43%) and good-quality blastocyst rates (60% versus 51%), although no differences in day-3 embryo quality, implantation or clinical pregnancy rates were observed.

4) Finally, limiting patient number in small two-chambered benchtop/top load units to a maximum of four patients, compared with the full unit ca-

Table 1- Differences between Box & Benchtop incubator

BOX TYPE INCUBATORS	BENCH TOP INCUBATORS
Occupy a lot of space in the lab	Occupy minimal space and can also be stacked one over the other
CAPEX is the same for Box/Benchtop Incubators	CAPEX is the same for Box/Benchtop Incubators
Running cost – Changing the Carbon inline filters, Decontamination cycle and CO2 cylinders	Running costs – Changing the Carbon Inline filters, Humidification flasks and triple gas cylinders.
Recurring costs are not very high	Recurring costs are higher in comparison with BOX incubators
Operates primarily with CO2 gas; Box incubators can be designed for triple mixture gas, but considering the big volume the gas cylinders empty pretty fast.	Primarily designed to function with Triple mixture gas.
Frequent Calibration is mandatory	Frequent Calibration is NOT mandatory. However, Annual external validation is recommended.
Specific Decontamination cycle is recommended at timed intervals to keep up the sterility	No such specific Decontamination cycle is recommended.
Higher risk for Fungal/Mold growth. This is due to the water bath at the bottom	Minimal risk for Fungal/Mold Growth
Heat transfer to culture dishes is by convection from air or water jacket controlled by a fan.	Heat transfer to culture dishes is by direct heat transfer from the heated stage at bottom and heated door at the top.
Owing to the larger volume, there is a risk of different temperatures at various points of incubator and a temperature mapping can be helpful for optimal culture.	Temperature is uniform all across.
Internal volume is very large and this is the major disadvantage of this incubator	Internal volume is small and this is the major advantage and aids in quick recovery of micro-culture environment.
Humidification is through the huge volume of water at the bottom of the incubator.	Humidification is through a flask that carries humidified air to the culture chambers

pacity of eight patients, has been used to improve blastocyst formation. Thus, IVF cases should be distributed between all available incubators to avoid overuse or excessive opening, regardless of the size or format of the incubator.
5) The use of 'holding' incubators that can be used for transient procedures, such as dish equilibration, sperm swim-up/capacitation and even brief culture of thawed embryos prior to same-day/immediate transfer. Using older 'outdated' incubators for these purposes may help avoid overuse of incubators that are used primarily for extended embryo culture.
6) Use of Benchtop incubators with Low oxygen culture system, seem to offer better reproductive outcomes.

SOME INCUBATOR DO'S AND DON'TS

1) Always read manufacturer manuals before placing the incubator into operation.
2) Always have a means to calibrate the incubator. Do not expect the incubator to come from the factory "ready to go to work."
3) Incubators are very sensitive. Perform timely quality checks through internal and external calibrations
4) Do not place any containers into the incubators that have an adhesive label on them; these will attract mould (unpublished observations). Do not place more plasticware in the incubator than is necessary; it may off-gas.
5) For the most part, the engineers for incubators have tried to think of everything, but they are not embryologists. Do not overlook the obvious. For example, engineers may not be aware of the sensitivity of gametes and embryos to position within the incubator or the effect that the numerous door openings have on embryo development.
6) Keep a running log of the changes and events associated with the incubator and the environment around the incubator. This will play a vital role in sorting out problems when they arise. Keep daily records of temperatures, CO_2 levels, and relative humidity of the incubator environment. Record these at about the same time every day.
7) If something does not seem right, it probably is not correct. Stop and get others involved to determine a course of action to correct the problem, if a problem exists.
8) Use the incubator company's technical support team. They have probably encountered many of the same problems you and I have encountered with incubators. If not, they may learn from the embryologist and build a better product in the future.

CONCLUSIONS

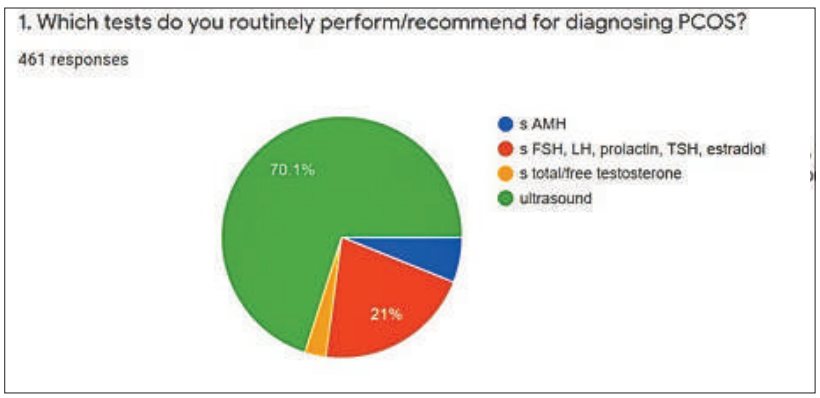
Incubator selection is an important decision for the IVF laboratory, as these devices regulate several environmental variables that can impact embryo development. While novel culture approaches may reduce the need for traditional incubators, for the time being they remain a central part of a modern IVF laboratory. Functional aspects of the incubator, such as gas capability and sensor type, as well

as temperature control and size/patient capacity need to be considered. Smaller incubator units, especially benchtop/top load devices, result in faster gas atmosphere and temperature recovery. However, no study has clearly demonstrated a distinct advantage of any specific incubator type in terms of human embryo development or clinical outcomes. Regardless of the unit, low-O_2 capability should be available and utilized and an IR CO_2 probe is preferable for those units that mix the gases to permit the fastest CO_2 recovery. Practical issues, such as cost and space, must also be weighed. The proper number and type of incubators to adequately support a laboratory's caseload must be determined on a laboratory-by-laboratory basis. A mix of incubator types, including both large-box, small-box and benchtop/topload within a laboratory helps cover multiple scenarios and offers several options for utilization, including implementation of emerging technologies.
Paramount in appropriate functioning and optimizing incubator performance is proper incubator management. Regardless of incubator size or the technology incorporated/utilized, improper management of case workflow or failure to perform proper quality control can compromise the culture conditions provided by any incubator. Management should consider the daily, rather than annual, patient caseload to help avoid overcrowding and maintain a stable environment. As technology continues to advance and new culture platforms and embryo selection technologies become available, incubators will undoubtedly need to be adapted to meet the changing needs of the field.

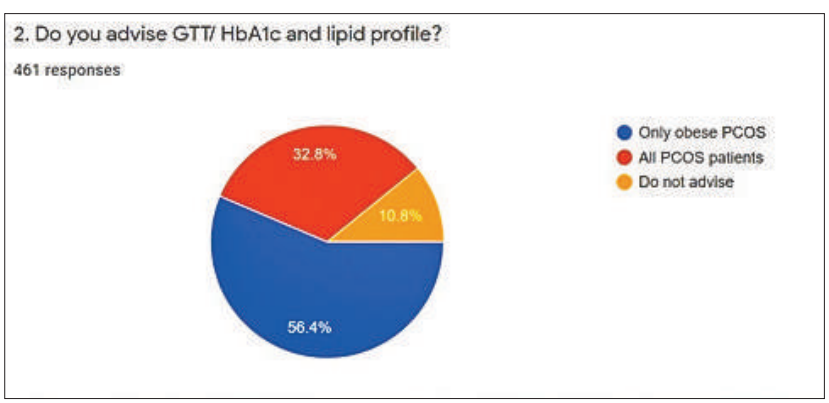
Dr Seema Pandey
Editor & Member Executive Committee, ISAR

ISAR PCOS SURVEY- AN ANALYSIS

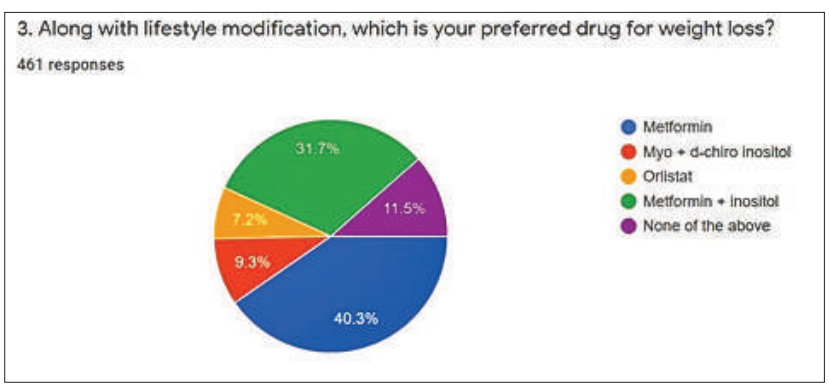
A survey regarding best clinical practice in the management of PCOS was done among the Indian practitioners, around 500 clinicians participated in this survey and following was their response to various questions along with correct answers.



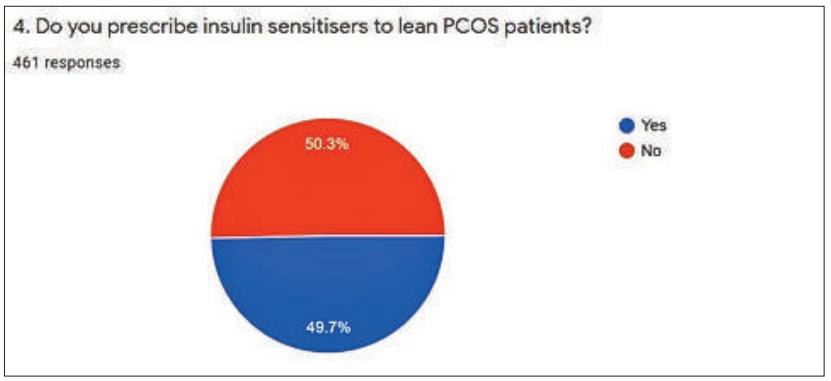
ANSWER -1 – CORRECT ANSWER 'C'
As per this survey around 70% of clinicians are relying on ultrasonography as the diagnostic tool for PCOS .
As per PCOS International guidelines 2018, PCOS is a clinical diagnosis and if you want to confirm the diagnosis only test recommended is calculated free Testosterone or free androgen index or calculated bioavailable testosterone. This option was chosen by only 5 % of clinicians.



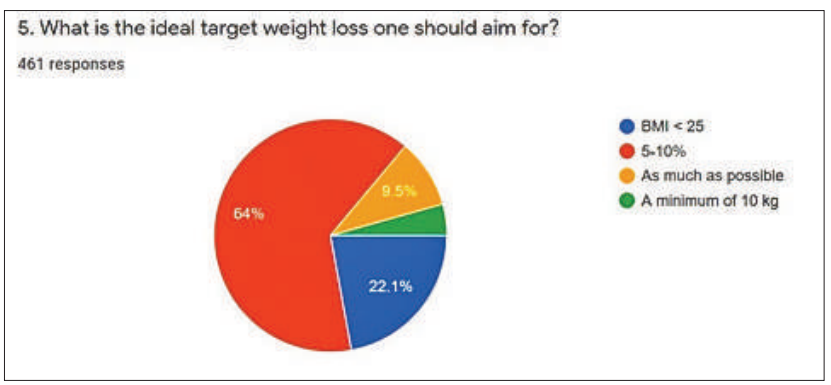
ANSWER – 2- 'A'-
Any woman regardless of her age with BMI>/= 25 (in Asians BMI>/= 23) has to undergo an Oral GTT and/or HbA1c as the chances of getting gestational diabetes, impaired glucose tolerance test & diabetes mellitus in PCOS women are significantly increased in than normal population. This risk increases further more if the woman is an Asian or American (5-fold in Asians, 4-Fold in Americans, and, 3-Fold in Europeans) and has a family history too. We are happy to share that >56% of us are doing OGTT & lipid profile in obese PCOS.



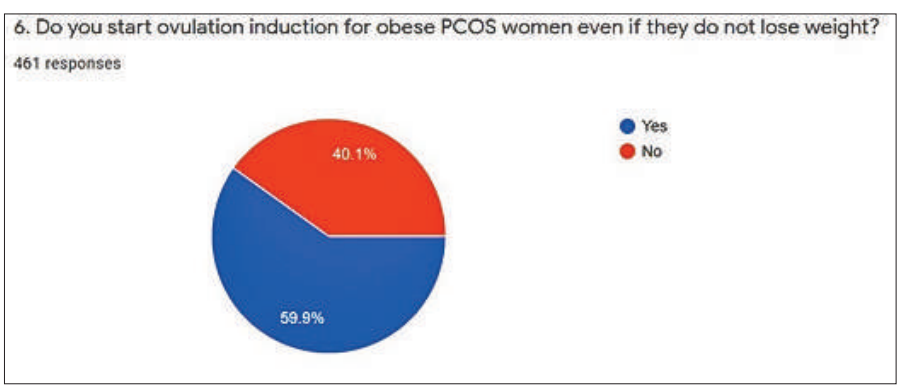
ANSWER-3- 'A'
If life style modifications in form of diet, exercise fails, then insulin sensitizer Metformin has to be added irrespective of the age.
>40 % of us are using metformin as the next line for management of weight loss if lifestyle modifications fail to work alone followed by the novel combination of metformin and myo-inositols for better and quick efficacy as both tend to act at different cellular levels.



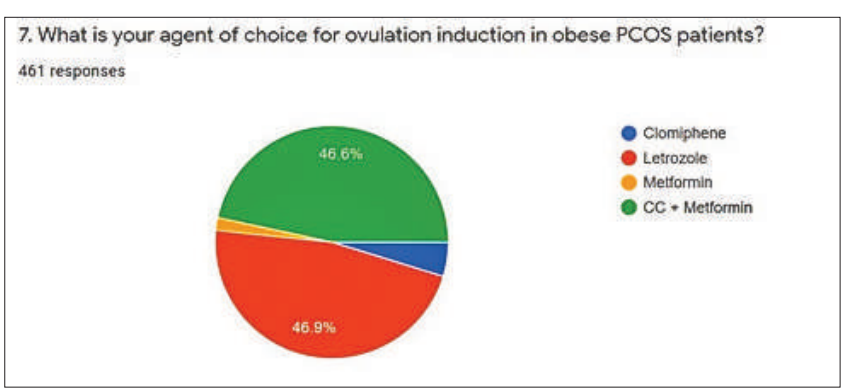
ANSWER-4- 'A'
Lean PCOS not responding to lifestyle modifications and medications directed towards treating the leading symptoms, insulin sensitizers are recommended.
We are happy to see that 50% of us agree that insulin resistance is inherent to most of the PCOS and they need insulin sensitizers despite being normal weight.



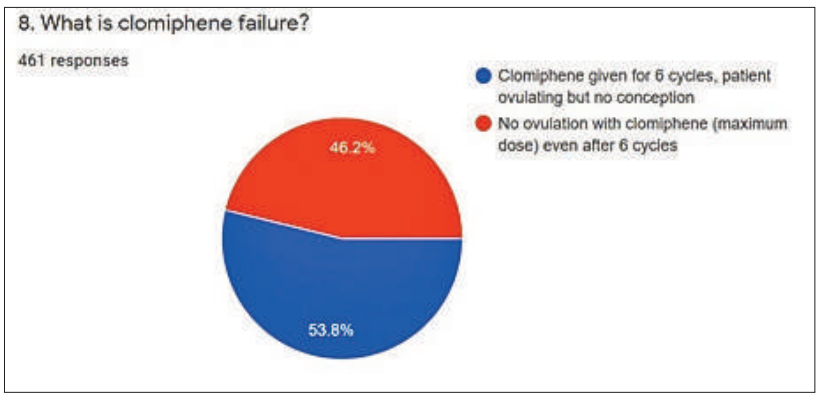
ANSWER-5- 'B'
Since reaching the ideal weight doesn't seem feasible and it was found that losing 5-10% of original weight lead to restoration of ovulation in around 40% of women.
64% of us believe in losing weight and setting a feasible goal so that our patient's compliant is good.



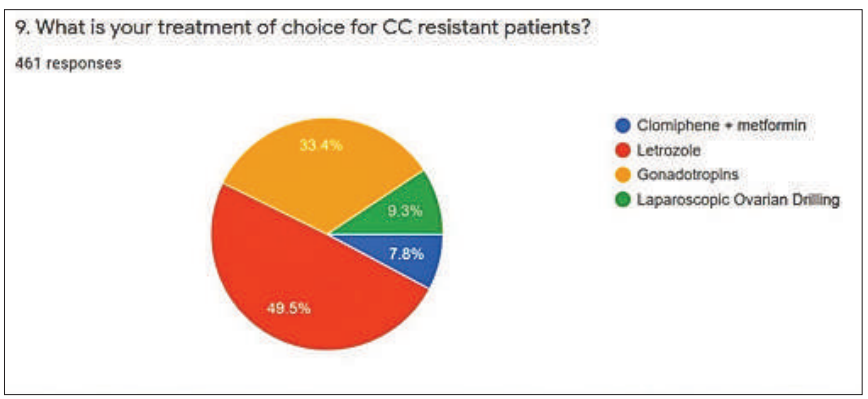
ANSWER-6- 'A'
Yes if woman is not able to lose weight and her BMI is below 35, we can induce her.
60% of participants believed that if a woman is not able to lose weight she should be offered ovulation induction after proper counselling.



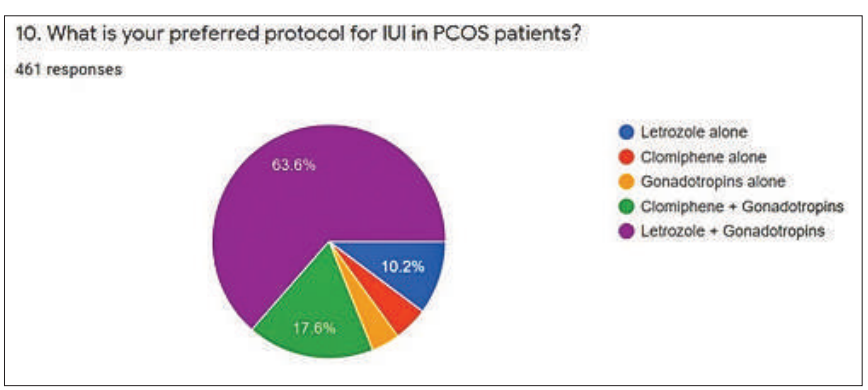
ANSWER-7- 'D'
As per international guidelines on PCOS-2018, CC+ Metformin could be used in preference, when considering clomiphene citrate or metformin
for ovulation induction in women with PCOS who are obese (BMI is>30 kg/m2) with Anovulatory infertility and no other infertility factors.
A recent review and meta-analysis favours letrozole for those obese PCOS whose metabolic derangement is not too much as letrozole improves live birth rates better than CC or metformin alone or in combination. But women with impaired GTT and obesity do better with cc+ metformin or letrozole + metformin. >40% of us are using letrozole as an alternative to CC in obese PCOS.



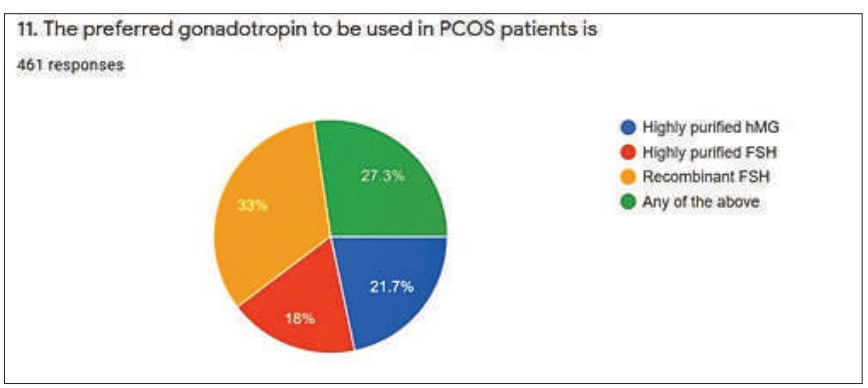
ANSWER-8- 'A'-
Woman ovulating with clomiphene but not conceiving, these women do better with gonadotropin stimulation with or without IUI.
>53.8% of the participants understand the concept clearly.



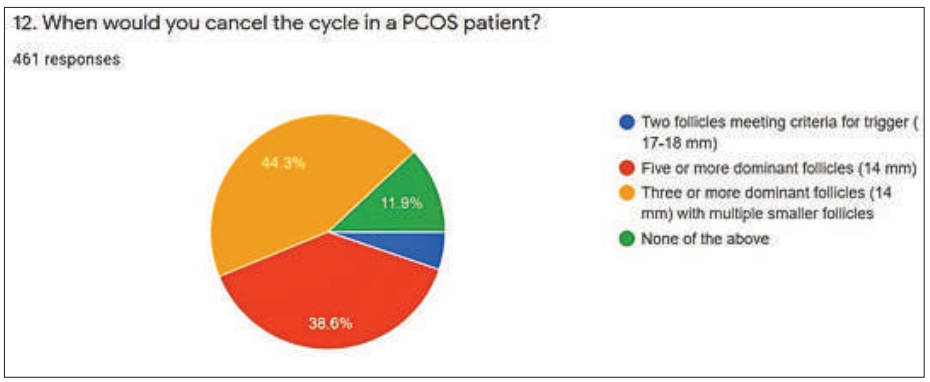
ANSWER- 9- 'C'
Gonadotrophins, where available and affordable, should be used in preference to clomiphene citrate combined with metformin therapy for ovulation induction, in women with PCOS with Anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates. (international PCOS-guideline 2018).
As per a network meta-analysis done in 2017, Letrozole was just after gonadotropins in list of preferences as its cost effective and has better patient acceptance rate.
We are happy to announce that 49.5 % of us are delivering the same.



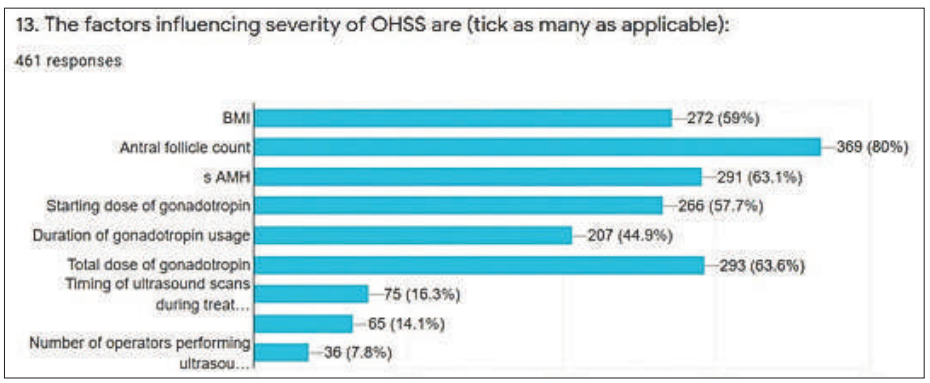
ANSWER-10- 'C'
The best results of IUI are with gonadotropins in terms of live birth rates.
63.6% of us in India are using letrozole + gonadotropins for doing IUI in PCOS patients.



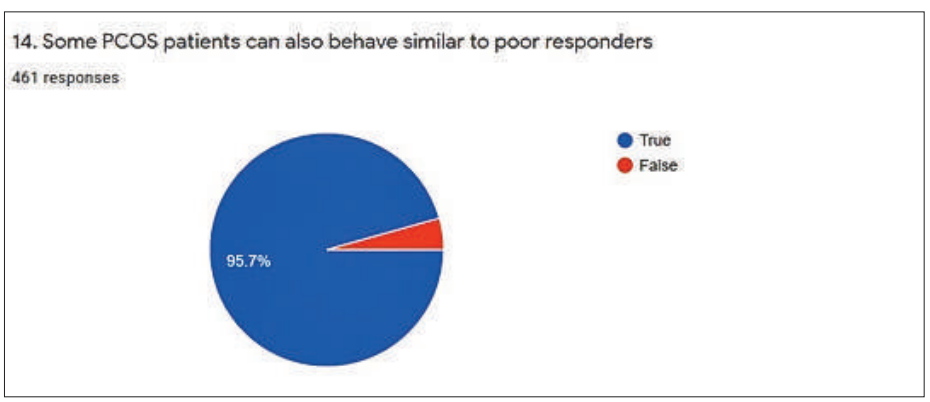
ANSWER- 11- 'D'
As per evidence any gonadotropin can be used, they don't change the clinical pregnancy rates and live birth rates. Only advantage with recombinant gonadotropin is ease of dose adjustment, purity and batch to batch variability.
33.0 % of clinicians who participated in this survey are doing the same.



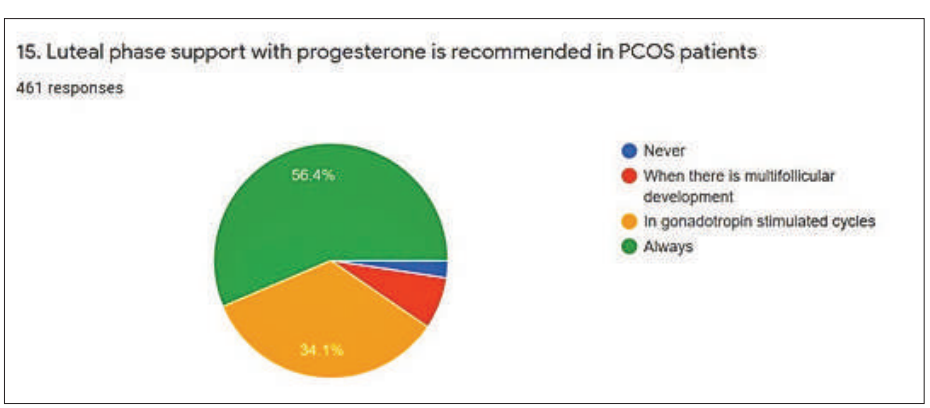
ANSWER – 12- 'C'
In any ovarian stimulation cycle if number of lead follicles is >3 or more and especially if these lead follicles are associated with multiple small follicles, these are silent contributors to raised estradiol and VEGF levels leading to OHSS along with increased chances of multiple pregnancies and these patients should be counselled regarding the consequences and the cycle should be cancelled.
In sync with our guideline, 44.3 % of participants apply the same criteria of cancellation.



ANSWER- 13-'A' 'B', 'C', 'D', 'E', 'F' 'G'
The most important factor in preventing OHSS is starting correct dose of gonadotropin as per ovarian markers like serum AMH and antral follicular count and BMI of the patient and if the dose can be decreased in time looking at the scan some damage could be prevented.
80% of participants rely on AFC, followed by serum AMH by 63 % of clinicians and 59% took BMI in consideration too. 57 % believed that starting dose of gonadotropins matter while 63.7% thought that total dose of gonadotropin was more important.



ANSWER-14- 'A'
PCOS with extremely high AMH and very high AFC are very tough to stimulate and need very high dosage of gonadotropins to break the threshold. These are known as resistant PCOS. Exact cause of this resistance is not known though but AMH acting like a strict gatekeeper and FSHG receptor polymorphism are few obvious reasons, if its due to FSH receptor polymorphism the threshold is broken but we require very high level of gonadotropin for that. 95.7% of us have come across this situation.



ANSWER- 15- 'C'
Administration of luteal phase progesterone is recommended in sub-fertile PCOS women undergoing OI or assisted reproduction (Grade A, EL 1). (Indian PCOS guidelines 2015)
56.4% of us are using regular luteal phase support in our PCOS women undergoing OI.

ESTROGEN THERAPY IN ART CYCLES FOR ENDOMETRIAL PRIMING

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INTRODUCTION

Human reproduction is possible only following successful implantation of a healthy developing embryo on the uterine endometrium. For this implantation to be accomplished there should be an absolute synchrony between the embryo and the endometrium. In a natural cycle, endometrial development is controlled by the hormonal secretions of the ovary. An estrogen primed endometrium is necessary for progesterone to act in modulating endometrial receptivity leading to a successful pregnancy. With the advent and progress of assisted reproductive technology (ART), endometrial priming has become the cornerstone for successful implantation.

The attainment of pregnancy in a woman with ovarian failure in 1983, launched a new era of understanding of endometrial receptivity, as an entity, that could be generated and controlled artificially. It is now clear that pregnancies can be achieved in women without ovarian function because estrogen and progesterone are apparently the only hormones that need to be supplemented or replaced to generate a receptive endometrial milieu. Estrogen replacement is essential for: a) endometrial development during frozen thawed embryo transfer (FET) in women with irregular anovulatory menstruations, b) endometrial development during oocyte and embryo donation (OD & ED) with poor or absent ovarian functions, and c) management of thin endometrium in ART.

There has been a dramatic increase in FET cycles in the last decade or so. That is largely due to the rising trend of following: a) excellent results of embryo freezing obtained by vitrification, b) elimination of OHSS risk by GnRH agonist trigger, c) elective single embryo transfer (eSET) practice, and d) preimplantation genetic diagnosis plus screening. However, for all these indications, estrogen replacement is required for endometrial priming, followed by progesterone replacement for optimum endometrial preparation.

A variety of regimens for the induction of endometrial receptivity have been described. These vary in the dose and route of administration of estrogen and progesterone, in the duration of estrogen administration before initiating progesterone, and in the duration of progesterone administration before embryo transfer. A recent Cochrane review concluded that there is "insufficient evidence to recommend one particular protocol for endometrial preparation over another with regard to pregnancy rate after embryo transfer". Nevertheless, it is worth considering the basic physiologic principles and ease of administration in deciding on a specific regimen of estrogen and progesterone replacement, especially in situations of poor response to stimulation towards endometrial development. In this article we will only discuss regarding estrogen therapy and its role in endometrial priming in ART cycles.

ESTROGENS

There are three major endogeneous estrogens namely estrone (E1), estradiol (E2), and estriol (E3). Among them E2 is the most potent and prevalent one in the systemic circulation of women. There are a large number of natural and synthetic estrogen preparations which are available for therapeutic use. Various preparations of natural estrogens include E2 valerate, E2 cypionate, E2 benzoate, E2 undecylate, and polyestradiol phosphate. E2 hemihydrate is the micronized form of 17-beta-E2, which diffuses easily through the cell membranes and therefore most rapidly absorbed on oral administration. However, ethinyl E2 is the widely used synthetic analogue, mainly in the oral contraceptive pills and not quite suitable for endometrial preparation with ART.

ROUTES OF ADMINISTRATION

There are various routes of administration of estrogen. **(a) Oral (b) Transdermal (c) Vaginal**

Oral route is the simplest of them all in usage and well tolerated in a standard dose. After oral administration E2 undergo extensive metabolism, initially in the intestinal mucosa and subsequently in the liver, where it is converted to E1 and E1 sulphate (E1S). This is called the "first-pass effect" on liver and as a result, E1 level gradually rises after oral estrogen administration and reach higher than E2. E1/E2 becomes abnormal with a ratio of 3 - 6 due to much higher levels of non-physiologic and less active metabolites (Fig 1 - 3).

Transdermal route is also acceptable, although some patients may find it little "messy". The area of application for the gel should be as large as possible (400-750cm2) over arms, shoulders, abdomen and inner thighs. It is allowed to dry for 5 minutes and bath is avoided for about one hour. However, the great advantage with this route is a steady level of E2. Since a minimum amount of E2 is converted to E1, most physiological E1/E2 ratio of 1 - 2 can be achieved,

similar to that in the follicular phase of natural menstrual cycles (Fig 1 - 3). This is largely due to the fact that, with this route, E2 is directly absorbed into the systemic circulation, unlike the "first pass" effect through liver following oral administration.

Vaginal route of estrogen mainly consist of estriol (E3), the most ineffective form, but it alleviates local menopausal symptoms. There is minimum or no systemic absorption and also results in a non-physiological E1/E2 ratio (Fig 1). Hence, this route is not effective for endometrial preparation in ART cycles.

Route of administration	E_1/E_2
Oral	3.0–6.0
Transdermal	1.0–2.0
Vaginal	0.2–0.4

Fig 1: Estrone/Estradiol (E1/E2) ratios by different routes of administration

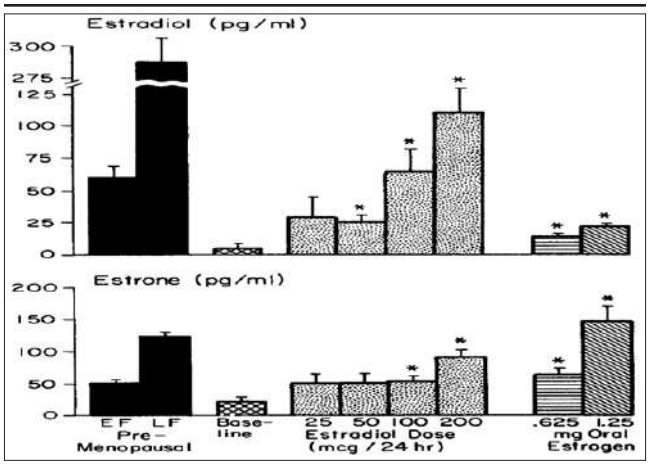

Fig 2: Serum Estrogen Levels with Oral and Transdermal Routes

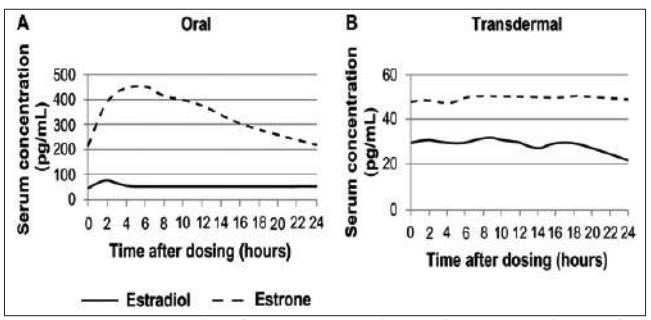

Fig 3: Serum Levels of E2 & E1 with Oral & Transdermal Routes

Different estrogens have varied relative binding affinities to the receptors (Fig 4). Hence, endometrium may react differently to the altered ratio of estrogens (E1/E2) and therefore circulating levels of E2 are more relevant to the efficacy estrogens on the endometrium.

Relative binding affinities of different estrogens for estrogen receptor α and estrogen receptor β.

Ligand	Estrogen receptor α	Estrogen receptor β
E_2 17β	100	100
E_2 17α	58	11
Estriol	14	21
Estrone	60	37

*Fig 4: Relative binding affinities of different estrogens on **α** & **β** receptors*

BIOLOGIC EFFECTS OF ORAL AND TRANSDERMAL ROUTES OF ESTROGENS

Oral estrogen therapy alters liver metabolism. It has adverse pharmacologic effects on hepatic proteins: 1) Renin substrate, 2) Sex Hormone Binding Globulin (SHBG), 3) Thyroxin Binding Globulin (TBG), 4) Cortisol Binding Globulin (CBG). It also leads to alteration of clotting factors and lipid profiles. These adverse effects makes oral route relatively contraindicated in women with cholelithiasis, hypertension, higher risk of intravascular clotting and venous thromboembolism. Oral estrogens are also vulnerable to the effects of hepatic enzyme inducers like psychotic drugs.

Transdermal estrogen therapy does not have such problems as it avoids "first pass effect" on liver by getting absorbed directly into systemic circulation. Hence, this route of delivery offers a greater level of safety. In addition, transdermal route delivers E2, the exact molecular form of estrogen that is secreted by the premenopausal ovary. Hence, more consistent serum E2 concentrations, without a high pharmacological level in liver can be achieved. However, a combination of oral and transdermal routes are more effective in women with thin endometrium and break-through bleeding, as the circulating level of E2 is much higher due to the combined effects.

Although E2 has been shown to be the most effective type of estrogen for endometrial priming in ART cycles, no consensus has been reached so far regarding the most appropriate route of therapy. Transdermal route produces most stable steady state levels in the physiological range along with a better E1/E2 ratio and has been suggested to be superior to oral route for the induction of endometrial receptivity [4]. There are however no evidence that any single regimen is better than other for 10 – 14 days of E2 replacement, either in constant or increasing dose, and may be further extended with inadequate endometrial thickness. Transdermal is more effective than oral route for inducing endometrial proliferation and may be a reasonable option for women who

fail to achieve an adequate response with oral route of estrogen therapy.

INDICATIONS AND REGIMENS OF ESTROGEN THERAPY IN ART CYCLES

The clinical uses of E2 in ART cycles include: 1) synchronisation and preparation of endometrium in FET as well as OD and ED cycles, 2) treatment of thin endometrium, and 3) as luteal phase manipulator in poor responders prior to ovarian stimulation with an aim to increase the number of oocytes by synchronisation of antral follicles.

Currently, FET is one of the most common components of ART and its success rate is at par with the fresh embryo cycles. E2 pre-treatment is mandatory for priming of endometrium for FET. Decades of ART with OD and ED cycle have revealed that E2 therapy is relatively simple and effective. It causes proliferartion of endometrial cells leading to increased thickness and also helps in induction of progesterone receptors to improve the endometrial receptivity. It also results in spiral artery contraction leading to lower oxygen tension in the functional endometrial layer, making the environment more favourable for embryo.

There are various regimens of E2 therapy used for endometrial preparation. A daily oral dose of 4 - 8 mg of E2 reproduces the serum levels and peripheral effects of E2 as seen in the natural menstrual cycle. It may be a variable dose step up regimen starting with E2 valerate 2mg once daily for 4 days, followed by twice daily for 4 days and then stepped up to thrice daily for 4 days or more. Otherwise, a constant oral dose of 6mg (2mg thrice daily) gives identical results and it's more convenient for the patients to remember. Similarly, a constant daily dose of transdermal E2 gel (0.06% w/w) 5gm, which delivers 6mg of E2, for 10 – 12 days is usually adequate for endometrial development. Progesterone is then added once the endometrial thickness reaches 7mm or more.

Several studies have shown similar pregnancy and live birth rates with either oral or transdermal E2 therapy in FET cycles. However, endometrial thickness was better and optimum endometrial development was achieved much earlier with lower dosage of E2 by transdermal in comparison to that with oral route. Hence, the risk of cycle cancellation was lower with transdermal route of E2 therapy. Women with primary ovarian failure due to Turner's syndrome, who have relatively smaller uterus with thin endometrium, respond better to non-oral E2 therapy during OD treatment.

ESTROGEN AND THIN ENDOMETRIUM

Estrogen supplementation can be used for the treatment of thin endometrium. One of the proposed regimens starts with a high dose (12mg or more, even up to 18mg daily) continuously from day 2 or 3 of menstrual cycle. Usually, 2mg dose is sufficient to block the hypothalamo-pituitary-ovarian-axis, so there is no need to add gonadotrophin analogues (GnRH), which may compromise endometrial vascular flow and proliferation. Another protocol suggested an extended use of estrogen therapy for 14 - 21 days to increase the endometrial thickness.

The pregnancy rate in the study group with a higher dose of estrogen therapy was significantly better than the control (38.5% vs 4.3%). A recent study on 40,000 embryo transfers on thin endometrium in fresh and FET cycles noted that clinical pregnancy and live birth rates decreased with each millimeter decline in endometrial thickness below 7 mm. However, there was no significant difference in pregnancy loss rates. On the other hand, uterine gene expression for embryo implantation is sustained at proper circulating E2 level and becomes refractory at higher E2 level needed for the treatment of thin endometrium. Thus window of implantation (WOI) remains open for a prolonged period if circulatory E2 levels are lower but rapidly closes at higher E2 levels. Similarly, a prolonged E2 exposure for endometrial preparation significantly lowers the live birth rate (LBR) and increases early pregnancy loss (EPL) after frozen-thawed blastocyst transfer. Hence, the choice of more effective transdermal route may reduce the need of a higher dose as well as prolongation of oral E2 therapy.

A Cochrane meta-analysis showed that type of E2 used and route administration had no effect on the success in ART cycles. In a randomized controlled trial (RCT), the endometrial thickness and clinical outcome were similar with either E2 tablets or patches. Another meta-analysis also revealed that the clinical pregnancy rates were similar but with transdermal route the miscarriage rate was lower along with a higher live birth rate. This was due to the asynchrony between embryo and endometrium, commonly found with oral route of E2 therapy.

CONCLUSIONS

Adequate endometrial thickness and receptivity is an essential component of human reproduction and thus are of great importance in the field of ART. Endometrial receptivity can be induced by exogenously administered estrogen and progesterone in a variety of different regimens. Estrogen priming results in endometrial proliferation and induction of progesterone receptors. Subsequent action on those receptors induces luteinization and the opening of the window of implantation. The degree of synchrony between embryo and endometrium influences the probability of embryo implantation and may be controlled by initiating progesterone supplementation at different times relative to the stage of embryo development.

Since estrogen priming of endometrium, in the vast majority of cases, can be achieved by a wide variety of methods, the simplest regimen may be the best initial approach in FET, OD and ED treatment cycles. In most cases, this would be an oral administration of a constant or increasing dose of E2 for 10 - 14days. If the endometrial priming is inadequate, a good second step is to change the dose and route of administration of estrogen with the intent of improving E2 delivery to the endometrium. Thus shifting toward a higher dose in oral route, along with a longer duration of therapy or opting for transdermal application with or without oral route should be done. Only when the priming is adequate, progesterone should be started, otherwise the treatment cycle may be cancelled.

The transdermal route of estrogen replacement therapy produces most stable steady-state levels of circulating E2. It is superior to the oral route for induction of endometrial proliferation and embryo receptivity in ART cycles. Transdermal route is a reasonable option for women who fail to achieve an adequate response with oral E2 therapy. It can therefore avoid the need for a higher dose or prolonged use of oral E2 administration In addition it is a much safer choice in women at high risk of venous thrombo-embolism and hyperlipidemia, as well as in those with hypertension and cholelithiasis, due to the avoidance of hepatic first pass effect.

VAGINAL PROGESTERONE IN PRETERM LABOR POST TOCOLYSIS

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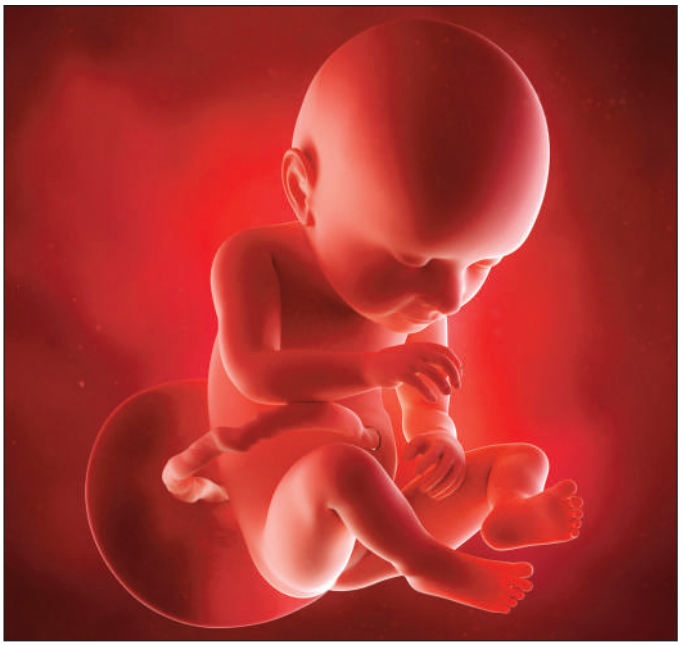
Preterm birth (PTB) (delivery prior to 37 weeks or 259 days of gestation) remains a significant problem in obstetric care, affecting women and babies world-wide. There are considerable health consequences for infants born preterm, as well as economic consequences for the health care system, individuals, and their families. It complicates 1 in 8 deliveries in the United States, but accounts for over 85 percent of all perinatal morbidity and mortality. Scenario is no different in India which experiences around 3.1 million preterm births annually and approximately one million are dying each year . This also results in significant psychological distress for parents and disruption of families as well as presenting a substantial economic burden for society. Premature neonates, especially those delivered <32 weeks' gestation, are at risk of complications which can result in extended stays in the neonatal intensive care unit and a requirement for resource intense interventions.

The prevention and treatment of PTB still remains one of the major challenges in obstetrics. Tocolysis is currently used in cases of preterm delivery (PTD), merely to enable administration of two doses of betamethasone with a 24-h gap for lung maturation (complete steroid cycle), which undoubtedly modifies perinatal outcome. Acute tocolysis over 48 h is an established "symptomatic" procedure. Pregnant women with threatened preterm labor (TPTL) and successfully treated with tocolytic therapy are at an increased risk of new episodes of PTD. After arrested preterm labor with acute tocolysis, maintenance tocolysis should be continued with the goals of prolonging gestation and improving neonatal outcome.



MAINTENANCE TOCOLYSIS – ROLE OF PROGESTERONE:

To date there has been no uniform and authoritative definition of "maintenance tocolysis/treatment". It is mostly understood to mean the continuation of drug-based tocolysis beyond 48 hours . There are several reasons to consider maintenance tocolysis. First, perinatal morbidity and mortality are inversely related to gestational age, therefore delaying delivery may improve perinatal outcome. Second, after an episode of preterm labor, the stimulus for preterm labor may remain and the patient remains at increased risk for preterm delivery .

Progesterone is an important agent for maintaining uterine quiescence. It is increasingly used in women at high risk for preterm labor and for maintenance tocolysis. Progesterone can be administered via oral capsule, vaginal gel or suppository, or intramuscularly. Oral administration has better patient compliance but there is variability in the plasma concentrations of the drug due to personal variation in gastric filling and enterohepatic circulation, while vaginal route results in higher local concentrations in uterus .

A retrospective study by Bomba-Opon DA, *et.al* evaluated progesterone efficacy in pregnant patients with preterm uterine contractions. 190 patient's records were included, wherein 94 women were treated with tocolytics and steroids (control group), while 96 women received additionally 200 mg of progesterone vaginally until delivery or 34th weeks of gestation (progesterone group). Results showed a significant increase in duration of pregnancy, in patients with premature uterine contractions, who received 200 mg of progesterone vaginally in addition to tocolytics in comparison to the control group (Table 1). Secondly,

they also found a reduction of deliveries before 34 weeks, decreased incidence of very low birth weight (<1500 g) and increased average birth weight only in patients who presented with premature uterine contractions after 27 weeks and then received vaginal progesterone after successful tocolysis.

Outcome	Progesterone group n-96	Treatment < 27 weeks n-34	Treatment ≥ 27 weeks n-62	Control group n-94	Treatment < 27 weeks n-26	Treatment ≥ 27 weeks n-68
Prolongation of pregnancy (weeks)						
Mean (SD)	7.6 (4.8)[b]	9.7 (6.5)	6.5 (3.1)[a]	6.3 (5.3)[b]	10.5 (6.5)	4.7 (3.8)[a]
Range	0–17	0–17	1–12	0–18	0–18	0–12
Gestational age at delivery (weeks)						
Mean (SD)	35	32.7 (6.4)	36 (2.5)[a]	34	34.2 (6.1)	32 (3.9)[a]
Range	(4.7) 22–40	22–40	30–39	(4.6) 24–40	24–40	27–40
Delivery <34 weeks: *n* (%)	22 (22.9)	16 (47.0)	6 (9.8)[a]	32 (34.0)	8 (30.8)	24 (35.3)[a]
Birth weight (g)						
Mean (SD)	2747 (955)	2352 (1266)	2963 (648)[b]	2570 (977)	2578 (1193)	2567 (921)[b]
Range	400–4580	400–4580	1380–3920	540–4100	540–4100	1020–3940
<2500 g – *n* (%)	28 (29.2)	14 (41.2)	14 (22.6)	40 (42.5)	10 (38.5)	30 (44.1)
<1500g – *n* (%)	12 (12.5)	10 (29.4)	2 (3.2)[a]	22 (23.4)	8 (30.8)	14 (20.6)[a]
RDS *n* (%)	12 (12.5)	7 (20.6)	5 (8.1)	24 (25.5)	16 (61.5)	8 (11.8)
Neonatal death *n* (%)	4 (4.2)	4 (11.8)	0	4 (4.2)	4 (15.4)	0

[a]$p<0.01$.
[b]$p<0.05$.

Table 1: Delivery and neonatal outcomes in progesterone versus control group

Another prospective, randomized controlled trial by Areia A et.al , evaluated that progesterone administration after successful tocolysis can prolong the latency period until delivery, reduce recurrence of TPTL and reduce fetal and maternal morbidity. 52 women with a singleton pregnancy between 24 and 34 weeks ' gestation, who had a proven PTD arrested successfully by tocolytic therapy with atosiban received 200mg vaginal progesterone or no therapy/placebo.

Results showed that the treatment group had a longer latency period until delivery and this was statistically significant (55 vs 38 days, p <0.024). Overall, study points to the benefits of the vaginal administration of progesterone, especially in prolonging latency period until delivery.

Groups	Progesterone (*n* = 26) *n*	(%)	Control (*n* = 26) *n*	(%)	*p* value	RR	95% CI
Latency period (days) (median, IQR)	55 (40.5–71.2)		38 (13–58)		0.02[§]		
Recurrence of pre-term labour	2	7.7	8	30.8	0.07	0.25	0.06–1.07
Gestational age at delivery (mean ± SD)							
Weeks	37.8 ± 1.1		36.6 ± 2.4		0.07[¶]		
Days	254 ± 24.7		246 ± 24.6		0.20[¶]		
Birth weight (g) (mean ± SD)	2,547 ± 642		2,628 ± 829		0.70[¶]		
Low birth weight	10	38.5	11	42.3	1	0.91	0.47–1.76
Respiratory distress syndrome	2	7.7	2	7.7	1	1.00	0.15–6.57
Fetal morbidity	5	19.2	6	24	0.67	0.83	0.29–2.39
Maternal morbidity	2	7.7	2	7.7	1	1.00	0.15–6.57

SD, standard deviation; IQR, interquartile range; RR, relative risk. [§]Mann–Whitney *U* test, χ^2 or Fisher's exact tests, [¶]Student's *t*-test.

Table 2: Primary and secondary outcome measures in women with pre-term delivery in progesterone versus control group

A prospective, randomized controlled study in Indian women by Mishra AA, et al4, compared safety and efficacy of micronized vaginal progesterone (group A) versus placebo (group B) as maintenance therapy to prevent ***preterm labor in 100 women with singleton pregnancy.***

	Group A (n=50)		Group B (n=50)		p-value
Gestational age (weeks)	**n**	**%**	**N**	**%**	
<37 weeks	4	8.0%	11	22.0%	0.129^{NS}
37-40 weeks	37	74.0%	33	66.0%	
>40 weeks	9	18.0%	6	12.0%	
Total	50	100.0%	50	100.0%	

Table 3: Gestational age at the time of delivery

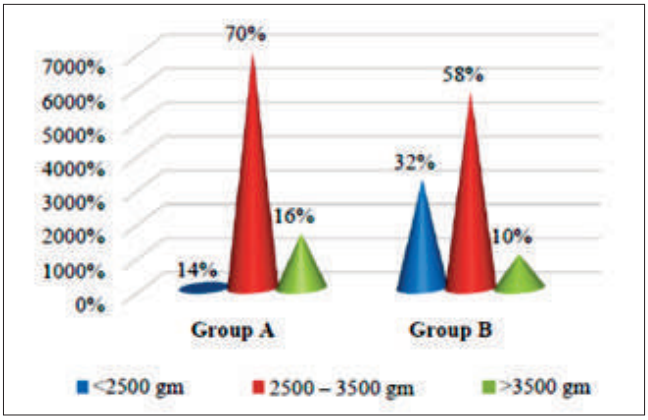


Figure 1: Intergroup distribution of birth weight

Results showed that analysis showed that women who were randomized to progesterone prophylaxis had significant increase in duration of pregnancy and mean of birthweight was higher in progesterone group (2963±36 gm) than placebo (2567±49 gm) which confirmed the positive effects of progesterone on increasing infants' weights at birth.

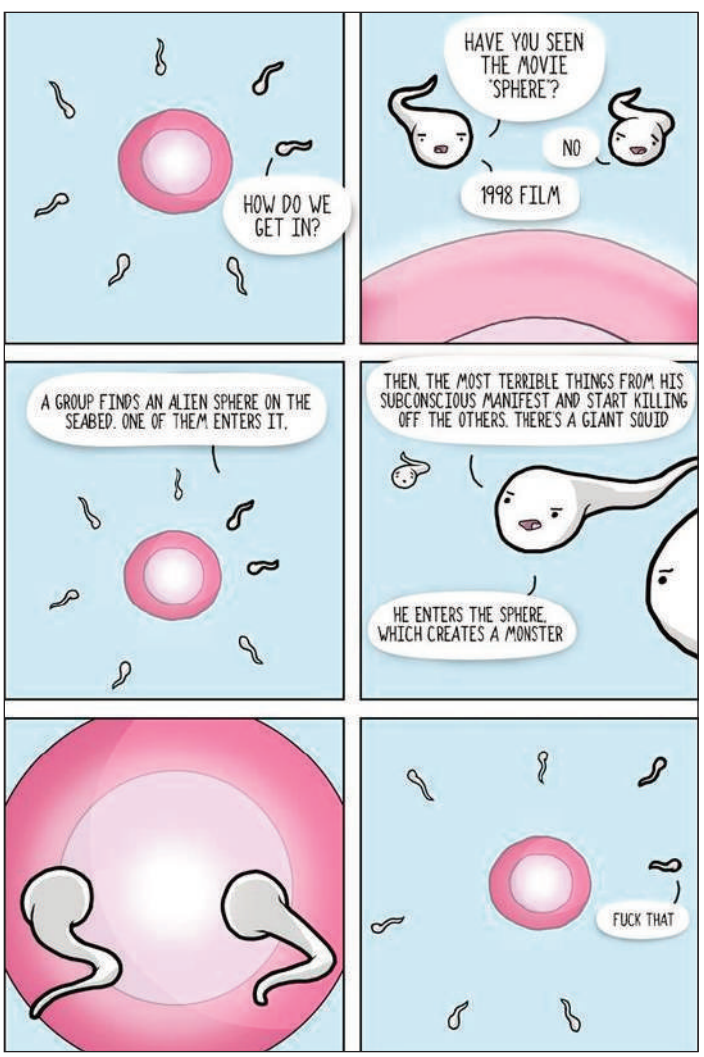
Hyett J, *et.al* , double blind randomized controlled study in 85 women who received either 400mg vaginal progesterone or placebo until 34weeks of gestation showed that Daily administration of 400mg vaginal progesterone after successful parenteral tocolysis may increase latency preceding delivery and improves cervical shortening and neonatal outcome in women with preterm labor.

A comparative study by Mohie-Eldin A, *et.al*, showed that progesterone has the upper hand compared to ritodrine in maintenance tocolysis. Further, vaginal progesterone reduces the rate of preterm labor, prolongs gestational age at delivery, reduces the frequency of uterine contractions, improves the symptoms of preterm labor and improves neonatal outcome with lower adverse effects.

Further a systematic review and meta-analysis by Ding MX, *et.al,* also showed that maintenance tocolysis with progesterone was effective for prolonging pregnancy and improving the birth weight of neonates for patients who had an episode of threatened preterm labor successfully treated with acute tocolytic therapy, whereas maintenance tocolysis therapy with nifedipine did not have the expected efficacy of pregnancy prolongation.

Preterm birth is one of the most common complications of pregnancy and prematurity is main cause of perinatal morbidity and mortality in many countries, accounting for at least one third of infant deaths. Overall, progesterone therapy has acceptable efficacy in prevention of preterm labor in terms of prolongation of delivery and by increasing gestational age at delivery. Further it also has positive effect on decreasing neonatal morbidity, mortality and on neonatal intensive care unit (NICU) stay.

HUMOUR



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JHRS ARTICLE REVIEW

THIS JOURNAL IS PUBMED INDEXED.

Singh N, Shekhar B, Mohanty S, Kumar S, Seth T, Girish B. Autologous bone marrow-derived stem cell therapy for Asherman's syndrome and endometrial atrophy: A 5-year follow-up study. J Hum Reprod Sci [serial online] 2020 [cited 2020 Dec 3];13:31-7. Available from: https://www.jhrsonline.org/text.asp?2020/13/1/31/281979

ABSTRACT

Background: Based on the role of bone marrow (BM) stem cells in regeneration of endometrium, refractory cases of Asherman's syndrome (AS) and endometrial atrophy (EA) may benefit with BM-derived intrauterine stem cell instillation.

Aims and Objectives: To evaluate the role of BM-derived autologous stem cell therapy in endometrial regeneration and restoration of menstruation and fertility in refractory cases of AS and EA.

Setting: This study was conducted at a tertiary care center. Design: This was a prospective, single-arm longitudinal study.

Materials and Methods: Twenty-five cases with refractory AS or EA were included. BM-derived mononuclear stem cells were instilled into the subendometrial zone followed by oral estrogen therapy for 3 months. Menstrual flow and endometrial thickness (ET) were assessed at 3, 6, and 9 months and 5 years.

Results: Statistical analysis was carried out using statistical software STATA version 12.0. Mean prestem cell transfer ET (mm) was 3.3 ± 1.0. At the end of 3 months, there was a significant increase in ET (mm) to 5.1 ± 1.9 (P = 0.001), but there was no significant change at 6 months (5.6 ± 1.5; P = 0.164), at 9 months (6.1 ± 1.7; P = 0.135), or at the end of 5 years. Six of the seven amenorrheic patients resumed menses. Three patients had a successful pregnancy outcome.

Conclusion: Intrauterine stem cell treatment is a promising novel approach for refractory cases of AS and EA.

EDITOR'S COMMENTARY:

This article addresses an important limiting factor for success in fertility treatments i.e. thin or damaged endometrium. The authors have conducted a prospective interventional study with a good length of follow up. As per international standards, the study has a clinical trial registry number and has a statement on ethics committee approval. The statistical analysis performed has been described adequately. The results are presented in an orderly and easily understandable manner. The authors have addressed the limitations of the study. All these are strengths of this informative article.

The limitations are that there is no statement on the sample size calculation. Asherman's syndrome is a relatively rare entity and recruiting a large sample size within a stipulated period of time understandably is difficult. However, a statement addressing this issue and the reason for not calculating the sample size also would have improved the quality of the article.

Refractory endometrium and its management is an important area of female infertility where proven therapies are very few. An improvement in the endometrial thickness, pregnancy and live birth is certainly a promising option. Multi-centre, prospective studies will go a long way in defining its place in the management of refractory endometrium.

Sardana P, Banker J, Gupta R, Kotdawala A, Lalitkumar P G, Banker M. The influence of delayed blastocyst development on the outcome of frozen-thawed transfer of euploid and untested embryos. J Hum Reprod Sci [serial online] 2020 [cited 2020 Dec 3];13:155-61. Available from: https://www.jhrsonline.org/text.asp?2020/13/2/155/289216

ABSTRACT

Objective: The primary objective is to compare live birth rates (LBRs) following frozen embryo transfer (FET) of euploid day 5 with day 6 blastocysts. We also compared LBRs following FET of untested blastocysts vitrified on day 5 and day 6 in self-oocyte and ovum donation (OD) cycles.

Design: This was a retrospective observational study.

Setting: Nova IVF Fertility, Ahmedabad. Materials and Methods: Ninety-seven FET using self-oocytes following preimplantation genetic testing A (PGT-A), 464 FET following OD, and 907 FET using self-oocytes without PGT-A testing between January 2016 and December 2017 were included in this study.

Main Outcome Measures: LBR following FET in day 5 versus day 6 blastocysts in euploid embryos using self-oocytes and in untested embryos using both self and donor oocytes.

Results: In PGT-A cycles, no statistically significant difference was observed in LBRs following transfer of euploid blastocysts developed on day 5 or day 6 (D5: 53%; D6:40%, P = 0.83). However, the LBRs with day 5 blastocysts were higher compared with day 6 group in untested group using both self and donor oocytes (self D5: 52.7%; D6: 38.2%; P = 0.001 and OD D5: 44.7%; D6: 29.8%; P = 0.001). Miscarriage rates were comparable in both the groups.

Conclusions: The present study demonstrated comparable pregnancy outcomes following FET of euploid embryos vitrified on day 5 and day 6. However, higher LBRs were reported in day 5 group in untested embryos.

EDITOR'S COMMENTARY:

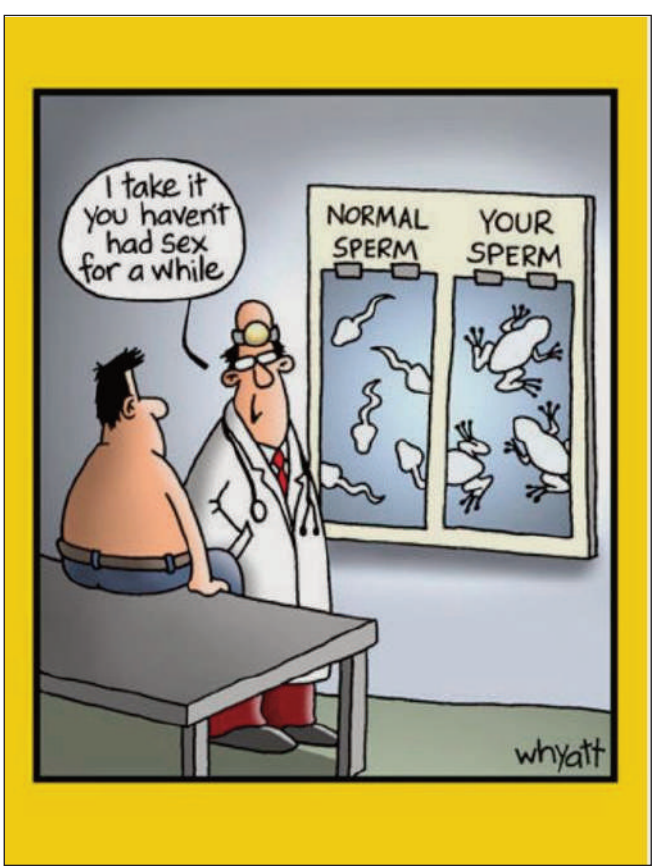
As we strive towards single blastocyst transfer, choosing the right embryo is of paramount important for success in IVF. This study addresses the outcome of frozen embryo transfer of day 5 vs day 6 blastocysts.

The study has a structured abstract and clearly defines the primary outcome measure as live birth rate. Multivariate analysis has been used to understand the importance of variables which may influence the results and their inference. The results do suggest that in the scenario of using embryos not subjected for PGT-A, a blastocyst transfer on day 5 yields a better live birth than that of a day 6 blastocyst. It also shows that a euploid blastocyst of day 5 or day 6 have similar live birth rate.

Three important aspects that need clarity are 1. the nature of the study - whether retrospective or prospective 2. A statement on ethics committee approval and 3. Sample size estimation.

The findings of this study, if validated by larger prospective studies will make an important contribution in decision making while choosing the blastocysts for FET.

HUMOUR



A WALK DOWN MEMORY LANE

Such a Pleasant Journey

Girish Nigudkar, Founder and CEO of InterMedics, reminisces about his 27 years of association with the IVF Industry in India.

It was sometime in Mid 1993 that I got a call from one of the doyens of our IVF field, Dr. Hrishikesh Pai, who having just returned from training with Melbourne IVF, asking for Cook Jansen & Andersen Embryo Transfer catheters and the Cook Royal Women's Hospital design echogenic tip OPU needles. We were just a year old company in medical devices then and more associated with Cardiology and Radiology divisions of Cook Medical. So, on getting this request from Dr. Pai, we scrambled to get these products from Cook Australia and our journey with the Indian IVF fraternity had begun.

To be honest, we did not at the time think that IVF held much potential in India, given the popular misconceptions that Indians were a fertile breed and need no help from IVF in that respect. The Government thought likewise and so did its best to discourage by imposing high customs duties to the tune of 140% on all IVF consumables and equipments. This was really unfortunate because it pushed up the costs very high, making it very difficult for both the IVF practioners and the patients to go in for infertility treatments. It took many years for the powers that be, to realise that infertility was also like any other ailment needing medical treatment for cure. If any thing, the problems faced by female patients are more acute in our country ;than in other places because of the stigma attached and harassment faced by women who are childless. Given the backdrop, it is to the immense credit of the pioneers of the late eighties and early nineties who chose to invest in and bring in the latest IVF treatment to the Indian patient. It was not easy going for both the practitioners and service providers, given that quality products had to be imported and the hurdles were many and the costs high.

We, at Intermedics, were lucky in having a reliable partner in Cook Medical who was one of the handful of quality IVF products manufacturers at the time. Even so, it was tough as costs were high and volume was low. So we gamely soldiered on to ensure that the IVF practioners got the products they required. In a couple of years in 1994 ISAR was established and the IVF practice in India gained momentum. By 1995 there were at least five major centres in Mumbai into regular IVF practice and a few had started in Delhi, Chennai and Bangalore. Some of the leading practitioners of that time like Dr Pai and Dr Jatin Shah from Mumbai and Dr Narendra and Jaideep Malhotra from Agra travelled as visiting doctors to various centres in other parts of the country did live cases there and in the process helped those doctors in setting up their own IVF practice. This process also greatly helped in accelerating the spread of quality IVF centres in different parts of the country.

Here are some of the important milestones that we passed by in our journey with the Indian IVF fraternity :

Year 1993 - supply commenced of the first IVF specific Embryo Transfer Catheters and Ultra Sound Guided OPU needles.

Year 1994 - A workshop was organised by Dr. Sadhana Desai at Bombay Hospital where Dr. Jansen fom Australia, part of the famous Jansen-Anderson duo, demonstrated the ET technique with their bulb tip design ET catheter. The response to that workshop and the enthusiasm shown by the participants was heartwarming, and showed signs of the promise that IVF held for the practioners in India. ISAR is established and the first national conference was held in Mumbai in November.

Year 1995 - ICSI as a technology had been developed and proven to improve IVF success rates dramatically. However, commercially manufactured quality ICSI pipettes were not available and IVF Centres were drawing their own glass pipettes which was laborious , time consuming, with technical imperfections which resulted in a lot of inefficiency. We introduced the quality controlled , commercially manufactured precision glass pipettes from Cook and the availability now of scientifically designed, technical perfect ICSI pipettes improved efficiencies and outcomes tenfold , which proved to be a great boon to the IVF practioners.

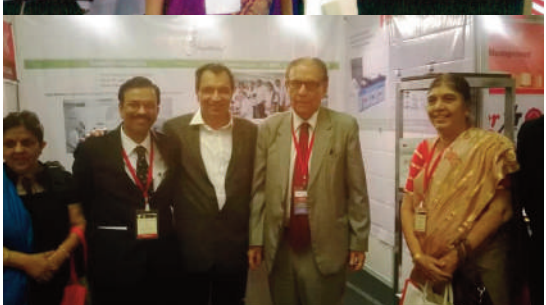
Year 1999 - COOK had introduced a year earlier their sequential culture media , which was a technological ad-

vancement over the single suite culture system available then. The first customers for us were Inkus IVF run by dr. Indira Hinduja and the late dr. Kusum Jhaveri and Dr Jatin Shah of Kamala polyclinic in Mumbai. However, with just two customers to start with and given the logistics of maintaining cold chain for a perishable product like the culture media, the costs were enormous . It was not a economically viable stream of business then but we gamely stuck on and slowly through seminars conducted by eminent embryologists and training workshops on the benefits of sequential media, we gathered more customers into our fold and soon became one of the top two media suppliers in the country. Sequential media also becomes the culture media of first choice and the Indian IVF market opens up to many more culture media brands

Year 2000 - COOK had introduced a Bench Top Incubator - the MINC a few years ago - specific for embryo culture and in India we were finding it difficult to introduce because of lack of quality pre- mix gas suppliers . However in Mumbai we could develop one triple gas mix supplier and soon we found our first customer in Dr Firuza Parikh at the Jaslok IVF center in Mumbai. It was difficult going initially, because Pre mix gas which was a prime requisite for the bench top incubator, was not easily available across the country. We had to coax speciality gas manufacturers in the metro cities of Mumbai, Delhi, Chennai and Bangalore to keep ready cylinders of a pre mix of CO2, N2 and O2 gases in the concentrations as required for embryo culture. There was reluctance on their part because this required that the contents of every cylinder that was filled with the pre mix gas be analysed and certified for quality assurance. It took us a good eight years to popularise the concept of bench top technology for embryo culturing and as late as 2007 there were only about 15 MINCS in the country. Today with the superiority of the benchtop technology firmly established - just 13 years later, we have close to a thousand MINCs and in every corner of the country (even as far away as in the states of Manipur and Nagaland in the North East) and we can take pride in the fact that we paved the way for many other brands of benchtop incubators to come into the Indian Market. With the widespread use of the IVF specific benchtop incubators for embryo culturing by the year 2010, you could say that the IVF market in India had indeed matured.

Year 2008 - Vitrification, a new highly efficient technology in cryopreservation becomes commercially available and we conduct numerous workshops and seminars across the country to train embryologists in this new technique with the specific media for the vitrification process.

Year 2010 – As in any discipline, quality education and hands on training in IVF is of paramount importance and even though many training centres for good embryology practice had already come up, we felt there was a need for a training school with a difference , so with the help of Cook we roped in the eminent embryologist and teacher, Dr James Catt from Australia who had been the Scientific Director at Sydney IVF and then Monash IVF and was in charge of training there as well, to be the director of training at our school – the Intermedics Training Academy (ITA). Dr James is an extremely patient and learned teacher and in the one week course trained upcoming and some experienced Indian embryologists in the entire gamut of embryology – from good embryology practices and ICSI to lab QC. We can proudly say that many of the young embryologists who trained under him and who had never handled ICSI machines before, are today renowned embryologists, successfully practicing in different parts of the country. It was expensive to get an Internationally acclaimed scientist of the calibre of Dr James Catt, but the ITA was established as a non profit training academy with the primary objective of providing quality embryology training of International standards to our practicing and aspiring embryologists.



As we journey along, we continue to see significant advances in IVF. Lasers for LAH and PGD, Time Lapse Imaging, CASA, all of which contribute to the better outcomes we see in infertility treatment today.

IVF in India has come a long way in these 27 years from a few cycles in 1993 to the more than 200,000 cycles today , and from the days of making home media and drawing glass pipettes to using lasers and timelapse imaging today. Going forward, as we continue our journey together, helping each other along the way through education, training and bringing in the latest technological advances in the field, one can only see a bright future and more exciting times for the Indian IVF fraternity.

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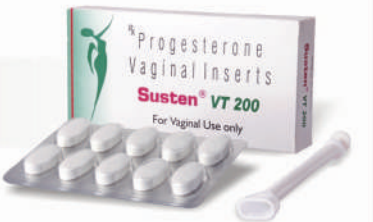

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Mirza F, et al. Dydrogesterone use in early pregnancy. Gynecol Endocrinol. 2016;32(2):97-106. † Schindler AE. Progestational effects of dydrogesterone in vitro, in vivo and on human endometrium. Maturitas. 2009;65(1):S3–S11.
^ Novel-Estradiol hemihydrate 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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