THE NEWSLETTER

isar EXPRESS

Indian Society for Assisted Reproduction

ISSUE 3, 2019

MYTHS AND CONTROVERSIES

Indian Society for Assisted Reproduction

25th ISAR 2020

ISAR 2020

Silver Jubilee Congress Of
Indian Society for Assisted Reproduction (ISAR)
6th-8th March 2020, HICC Hyderabad India

TSAR

Hosted by
Telangana Chapter of ISAR (TSAR)

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Obstetrics & Gynaecological Society of Hyderabad

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Menopur (HP – hMG) delivers more live births versus rFSH[1]

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Composition: Menopur® 75 IU: Each vial with powder contains highly purified menotropin (human menopausal gonadotropin, HMG) corresponding to follicle stimulating hormone activity FSH 75 IU and luteinizing hormone activity LH 75 IU. **MENOPUR® multidose 600 IU:** Each vial with powder contains highly purified menotropin (human menopausal gonadotropin, HMG) corresponding to follicle stimulating hormone activity FSH 600 IU and luteinizing hormone activity LH 600 IU. **MENOPUR® multidose 1200 IU:** Each vial with powder contains highly purified menotropin (human menopausal gonadotropin, HMG) corresponding to follicle stimulating hormone activity FSH 1200 IU and luteinizing hormone activity LH 1200 IU. **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 MENOPUR® 600 IU and 1200 IU are 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:** Tumors 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 tumors 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. **Shelf Life:** MENOPUR® 75 IU - 2 years. For immediate and single use following reconstitution. MENOPUR® 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 prefilled syringe for reconstitution, 1 needle for reconstitution, 9 alcohol pads and 9 disposable syringes for administration graduated in FSH/LH units with pre-fixed needles. MENOPUR® multidose 1200 IU: 1 vial of powder, 2 prefilled syringes for reconstitution, 1 needle for reconstitution, 18 alcohol pads and 18 disposable syringes for administration graduated in FSH/LH units with pre-fixed needles.
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Manufactured by: MENOPUR® 75 IU – Ferring GmbH, Germany
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Imported & Marketed by: Ferring Pharmaceuticals Pvt. Ltd., Thane-421302, India
For additional information on prescribing information, kindly refer to the package insert.
Date of Preparation: 2nd August 2018

References: 1. Menopur Prescribing Information

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EDITORIAL

Subfertility in the past has traditionally been an area of medicine in which physicians had limited means to help their patients. The scenario changed dramatically with the birth of the world's first in vitro fertilization (IVF) baby, Louise Brown, in 1978. The importance of this birth to scientists, clinicians, and subfertile patients cannot be overstated. Within decades, IVF made a frog leap by exploding its narrow, circumscribed domain to become available worldwide. This resulted in constant paradigm shifts that required frequent social and ethical evaluation by professional bodies. The fact that treatment options for subfertility tend to lend themselves towards controversy is well justified, given the sensitive nature of the work and responsibilities that clinicians hold. Along with the developed nations, India too needed to buckle up its process of rapid government legalisation and carry out regular audit of clinical work in keeping with the fast pace of advanced fertility treatment. For, if regulations lag behind clinical advancement, professional misconduct and commercial exploitations are bound to follow closely on heels.

The interplay of technology and human reproduction has always been a matter of controversy. When artificial insemination was first discovered a century ago, the procedure was widely viewed as scandalous. Similarly, forty long years have now gone by and IVF is still the byword for controversy! Morally, it remains a divisive topic even in the western world where 12 percent of adults in the United States think IVF is wrong, 33 percent find it to be acceptable, and 46 percent are indifferent. Complicating the issue is the fact that, unlike frozen sperm or eggs, there's a tendency to view frozen embryos as something more than just a reproductive asset. There are patients who believe with their heart that these are their frozen children.

It must be mentioned that although India was quick enough to replicate the feat with the birth of the second IVF baby, Durga in October 1978, as opposed to the UK, it is primarily a heterogeneous country where old social constructs nestle comfortably alongside the western technological advancement. Little wonder therefore, unlike the highly publicised birth of Louise Brown, Durga's birth was shrouded in secrecy and controversy. The parents of Durga were loathe to publicise their clinical care and the subsequent birth of their daughter. As a result, deep suspicions were aroused about the integrity of Dr Subhas Mukherjee's path breaking work leading to the sad outcome of him committing suicide.

So what happens to a country like India as far as Assisted Reproductive Technology (ART) is concerned? Well, for a start, unending number of myths and misconceptions abound. Special mention may be made to the major ones: a) babies conceived will have a higher chance of birth defects, low birth weight or developmental delays; b) 'one size fits all' approach and the only option for couples struggling with subfertility; c) always leads to multiple births and sometime couple come for ART to have twins; d) needs bed rest for 9 months, e) it is the last resort for infertile couples and always works! To add to all these, the phenomenal cost of bearing the burden of this treatment can never be overstated in a poor country like India. ART can only be made acceptable by all and sundry if mindset of the people undergo sea change along with the existing protocol. More importantly, the Cash before Care concept also needs to take a backseat to popularise it.

As if these are not enough, clinicians too, are divided in their opinions regarding the various treatment plans for PCOS, endometriosis and male infertility in the absence of any standard uniform protocol. Although significant progress has been made towards the development of universally accepted diagnostic criteria called PCOS, the optimal treatment for infertile women with for this enigmatic syndrome has not yet been defined. Various interventions have been proposed ranging from lifestyle modifications, administration of pharmaceutical agents, insulin sensitizing agents, gonadotrophins the use of laparoscopic ovarian drilling and the application of ART. Infertility treatments for patients with endometriosis too, need special consideration. Surgery and ART cross over according to the different stages of the disease and the patient’s age. Minimal and mild disease frequently benefit from conservative surgery whereas advanced, moderate and severe stages usually require ART.

Again, the management of the infertile male remains difficult as, in a significant proportion of men, the cause of the infertility remains unclear. The major frustration for the clinician managing infertile men is the fact that in 40–50% of cases, while the sperm defect can be defined, no specific cause can be found, designating these to the category of idiopathic spermatogenic defects. It is true that the use of ICSI has expanded the capability of achieving fertilization from sperm recovered either from the epididymis or directly from the testis. Although this success is dramatic, there is some need for caution and discussion to fully understand certain implications. The identification that significant numbers of men have deletions in the Y chromosome raises the possibility that male offspring, achieved through ICSI, maybe affected by the Y chromosome deletions transmitted from their father. The jury is still out on this finding that raises the need for the use of pre-ICSI screening of the Y chromosome in infertile men with sperm counts of less than 5 million/mL.

Fertility experts are yet undecided on whether to transfer a fresh or frozen embryo to a patient's womb in creating healthy babies. Unfortunately, there exists no one-size-fits-all solution. The best technique may vary, depending on how many eggs the patient produces and the nature of the endometrium. ART can be very successful treatment but many cycles don’t have successful implantation, even after several transfers with apparently good quality embryos. Also, sometimes treatment achieves a conception, but the pregnancy doesn’t develop to term. At the end of the day, both clinicians and embryologists are saddled with the burden of sharing the blame if the treatment is unsuccessful. One gets accused for not bringing the embryo to a perfect stage for implantation while the other is criticised for failing to prepare the uterus so as to make it ready for bearing the pregnancy. So, as far as sharing a collective responsibility is concerned, it must be borne in mind that the entire ART community is constantly treading on thin ice. Therefore the motto of our fraternity ought to be: Come whatever may, we need to swim and sink together.

In this issue of ISAR Express, we present many such Myths and Controversies related to ART. We hope these articles would provide you ample thought for further research and also motivate you to modify your treatment protocols in the near future.

Our sincere thanks to ISAR President, Dr Jaideep Malhotra for giving us the opportunity to edit this issue.

Wishing everyone a Happy 2020 and Happy Reading!

Dr Gautam Khastgir
Editor

Dr Neha Priyadarshini
Editor

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MYTHS & CONTROVERSIES

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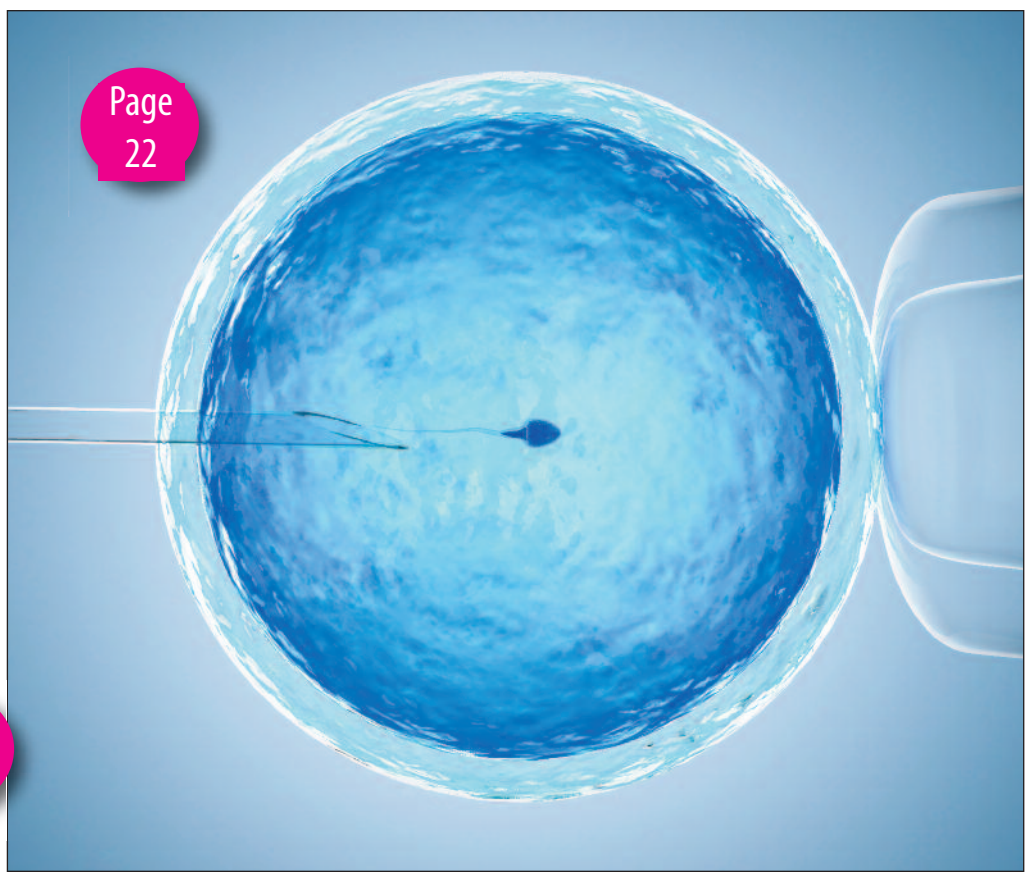

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In women undergoing controlled ovarian stimulation

Gonapress®

Cetrorelix Acetate for Injection 0.25 mg

- Prevents premature LH* surge[1]
- Reduces the incidence of cases of OHSS[2]
- Results in similar pregnancy rates as the long agonist protocol[2]

Dosage

Subcutaneous injection (0.25mg) on either stimulation day 5 or day 6, continued daily until the day of hCG* administration[1]

Gonapress®
Cetrorelix Acetate for Injection 0.25 mg
For Subcutaneous Use Only
Abbreviated Prescribing Information
Composition: Each Combipack contains 1 vial of Cetrorelix Acetate for Injection (Lyophilized) & 1 ampoule of 1ml Sterile water for injections IP. ***Each vial contains*** Cetrorelix acetate equivalent to Cetrorelix 0.25 mg, excipients q.s. **Indications:** GONAPRESS® is indicated for the inhibition of premature LH surges in women undergoing controlled ovarian stimulation. **Dosage & Administration**: GONAPRESS® should only be prescribed by a specialist experienced in this field. It has to be injected subcutaneously into lower abdominal wall. Ovarian stimulation therapy with gonadotropins (FSH, hMG) on cycle day 2 or 3. The dose of gonadotropins should be adjusted according to individual response. GONAPRESS® should be administered subcutaneously once daily during early to mid-follicular phase. GONAPRESS® is administered on either stimulation day 5 (morning or evening) or day 6 (morning) and continued daily until the day of hCG administration. When assessment by ultrasound shows sufficient number of follicles of adequate size, hCG is administered to induce ovulation and final maturation of the oocytes. No hCG should be administered if the ovaries show an excessive response to the treatment with gonadotropins to reduce the chance of developing ovarian hyperstimulation syndrome (OHSS). *Instructions for administration*: GONAPRESS® should only be reconstituted with the solvent provided (Sterile water for injections). Aseptically withdraw the entire contents of the diluent ampoule into the syringe. Push the needle through the center of rubber stopper of the appropriate GONAPRESS® vial and slowly inject the solvent into the vial. Leaving the syringe in the vial, gently swirl the vial until the solution is clear and without residues. Vigorous shaking with bubble formation should be avoided. Draw the total contents of the vial into the syringe, if necessary invert the vial and pull back the needle as far as needed to withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 0.23 mg Cetrorelix. Do not use if the solution contains particles or if the solution is not clear. The solution should be used immediately after reconstitution. The injection site should be varied daily when being used in the multiple dose regimen. **Contraindications:** Moderate to severe hepatic impairment; moderate to severe renal impairment; hypersensitivity to Cetrorelix acetate or extrinsic peptide hormones or mannitol; known hypersensitivity to GnRH or other GnRH analogs; known or suspected pregnancy and lactation; post menopausal women. **Warnings and Precautions:** Cetrorelix acetate for injection should be prescribed by specialists experienced in fertility treatment. Exclude pregnancy before starting treatment with Cetrorelix. Should not be prescribed if patient is pregnant. Caution is advised in patients with hypersensitivity to GnRH. Special care should be taken in patients with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with Cetrorelix is not advised in women with severe allergic conditions. Cetrorelix should be used in repeated cycles only after careful risk/benefit evaluation. Prior to therapy with Cetrorelix acetate for injection patients should be informed of the duration of treatment and monitoring procedures that will be required. **Adverse Reactions**: Local reactions at the injection site (erythema, redness, bruising, itching, swelling and pruritus) have been transiently reported and of mild intensity. Rare cases of hypersensitivity including pseudo allergic/ anaphylactoid reactions, nausea and headache. Mild to moderate ovarian hyperstimulation syndrome (WHO grade I or II) which is an intrinsic risk of stimulation procedure. *For more details on undesirable effects, please see package insert.* **Overdosage:** Overdose in humans may result in prolonged duration of action but is unlikely to produce acute toxic effects. No reports of overdosage with Cetrorelix injections in humans.
Incompatibilities: As Cetrorelix is incompatible with several substances of common parental solutions, it should be dissolved only by using the supplied sterile water for injections. **Storage:** Store between 2 deg C to 8 deg C. Do not freeze. Protect from light. Keep out of reach of children. **Presentation & Pack Size**: Vial containing 0.25 mg lyophilized powder for injection of Cetrorelix acetate along with ampoule containing 1 ml of sterile water for injections IP as diluent.
SCHEDULE H PRESCRIPTION DRUG - CAUTION
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Manufactured by: Gufic Biosciences Limited, Gujarat.
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For full information on prescribing information, kindly refer to the package insert.
Date of Preparation: 30 August 2018

Reference: 1. Gonapress Prescribing Information 2. Ludwig M, Katalinic A, Diedrich K. Arch Gynecol Obstet. 2001;265(4):175-82
*LH - Luteinizing hormone *hCG - Human Chorionic Gonadotropin *OHSS - Ovarian hyperstimulation syndrome

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MYTHS &
CONTROVERSIES

Dear Isarians,

The month of lights, has just passed by and what better tribute can I pay, to all of you, who are bringing light into many lives.

All hell broke loose, with the birth of the first IVF baby on 27th of July 1978, who was at the receiving end, the two men, who made the breakthrough, orchestrated the science behind the in-vitro fertilisation. It was not an easy journey for them, before and after. Their fraternity condemned them, the society condemned, the religious leaders condemned them, media sensationalised it, but today this technology has brought light into the lives of millions across the world and that's why, this issue is dedicated to those who spread joy and happiness.

Inspite of millions of babies born through the technique all over the world, the controversies and myths surrounding ART are endless and everyday something new crops up. This too shall pass as,

"The Passionate controversies of one era, are viewed as sterile preoccupation by another, for knowledge alters what we seek as well as what we find." ***Freda Adler.***

It all started with IVF, moving on to ICSI, Third party reproduction, surrogacy, cloning, designer babies, uterine transplant, to gene editing, what has not been controversial and surrounded by endless myths in ART, but at the end of the day,

As ***Peter Singer*** puts it, **"Deeply controversial at first, IVF has fought back ethical and religious objections to become commonplace".**

Because it brings in joy, happiness and peace to millions of infertile couples all over the world, it makes them complete and that's why, no one could fight the goodness of the technique and technology. If you hold a baby in your arms, that began it's journey in a dish, I am sure people will have a lot to smile. But to bring those smiles, crossing all ethical or moral boundaries will raise a lot of controversies and surround us with many barriers and myths.

Sometimes we do feel under the weather and exploited, but I would rather feel like ***Roald Dahl*** and say, **"My candle burns at both ends it will not last the night but aah my friends and oh my foes it gives a lovely light"**

My sincere thanks to **Dr Gautam Khastgir** and **Dr Neha Jha** for all the hard work put in the preparation of this issue and also to **Father of IVF** in our country **Dr B N Chakraborty** for enlightening all of us with his journey and the light. I am sure, you will find many interesting articles in this issue to keep you glued and wait for the next issue.

Dear Friends, Keep on doing the good work, till we meet again to light many candles together.

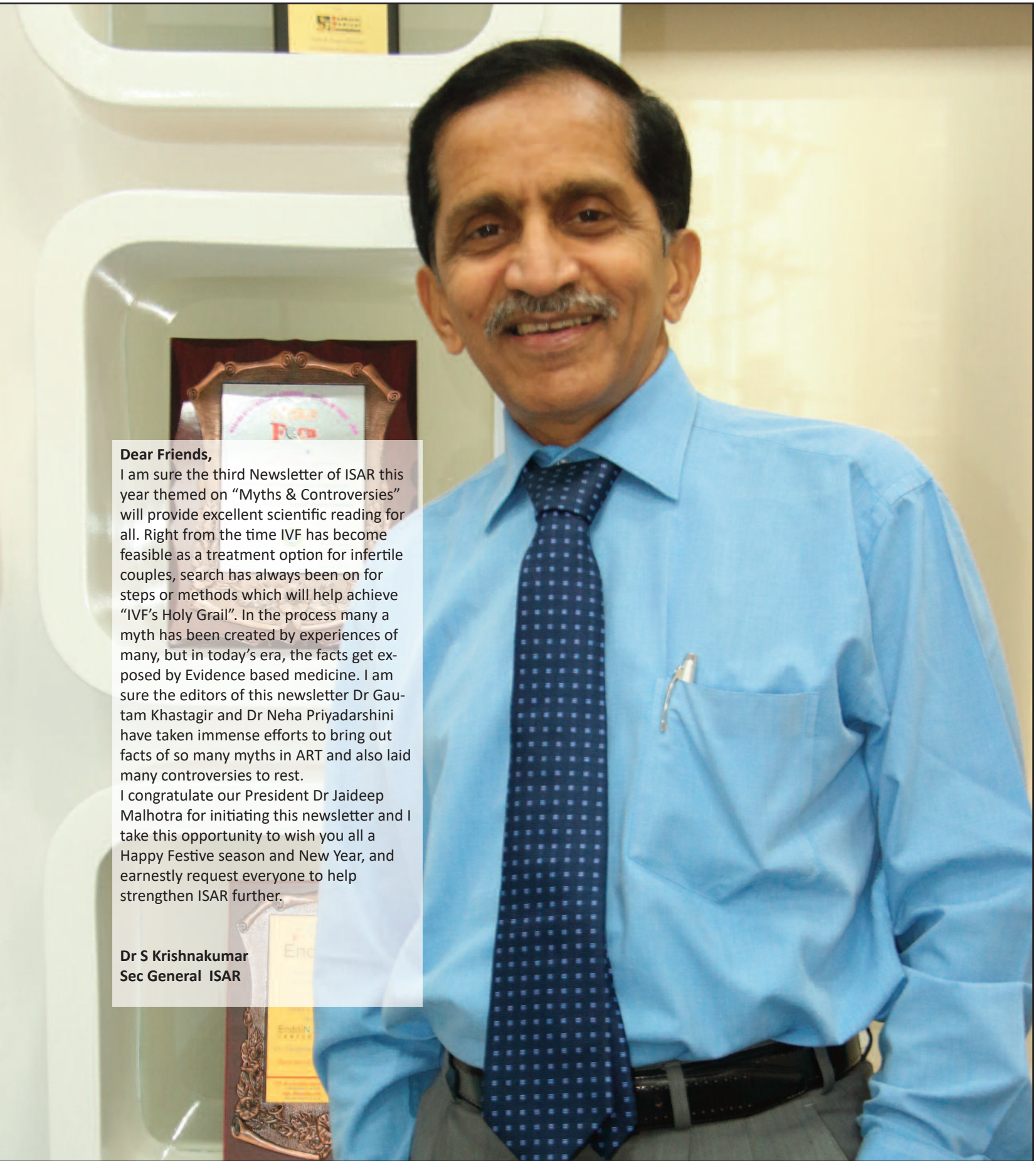
Dr Jaideep Malhotra
President ISAR

ABOUT ISIS

Isis was the ancient Egyptian goddess of fertility and was also known as the goddess of motherhood, magic, death, healing and rebirth. Isis was the first daughter of Geb and Nut who were the god of the earth and the goddess of the sky. Isis was the sister of Osiris who later on became her husband as well. The son of Isis and Osiris was Horus.

MYTHS & CONTROVERSIES

SECRETARY GENERAL'S MESSAGE



Dear Friends,

I am sure the third Newsletter of ISAR this year themed on "Myths & Controversies" will provide excellent scientific reading for all. Right from the time IVF has become feasible as a treatment option for infertile couples, search has always been on for steps or methods which will help achieve "IVF's Holy Grail". In the process many a myth has been created by experiences of many, but in today's era, the facts get exposed by Evidence based medicine. I am sure the editors of this newsletter Dr Gautam Khastagir and Dr Neha Priyadarshini have taken immense efforts to bring out facts of so many myths in ART and also laid many controversies to rest.

I congratulate our President Dr Jaideep Malhotra for initiating this newsletter and I take this opportunity to wish you all a Happy Festive season and New Year, and earnestly request everyone to help strengthen ISAR further.

Dr S Krishnakumar
Sec General ISAR

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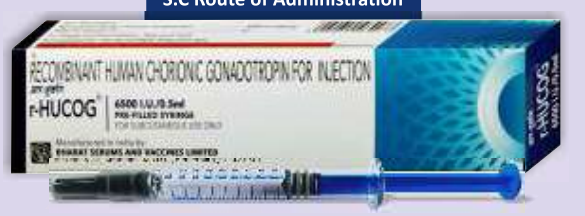

Reference: 1. Majumdar A. et al. J Hum Reprod Sci 2019;12:53-8 2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021149s020lbl.pdf as accessed on 14/09/2018 ~Assisted Reproduction Techniques * Refer pack insert for more dosage regimen

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1. Genazzani, et al. "Modulatory role of D-chiroinositol (DCI) on LH and insulin secretion in women with PCOS". Gynecol Endocrinol. 2014 2. Gynecol Endocrinol, 2015; 31(1): 52–56
3. Data on file. *Assisted reproductive technology #D-Chiro Inositol *Llaneza et al. Comparison of the effect of two combinations of myo-inositol and D-chiro-inositol in women with polycystic ovary syndrome who undergo ICSI. ESHRE annual meeting 1 – 4 July 2018.

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YALE STUDY EXAMINES SHIFTS IN FERTILITY RATES AMONG GENERATION X WOMEN

A new study examines shifts in fertility behaviors among Generation X women - those born between 1965-1982 - compared to their Baby Boomer counterparts, and explores whether the fertility of college-educated women is increasing more quickly across cohorts in Generation X than the fertility of their less educated counterparts.

The study, published online in the journal *Population Studies*, used data from the National Survey of Family Growth to determine educational differentials in fertility levels and timing across four 5-year cohorts. The study shows that total fertility rates (TFRs) increased across all educational groups in Generation X women -- with the greatest increase seen in college-educated women.

Emma Zang, assistant professor in the Department of Sociology who authored the study, found that the increase in the fertility rates for college-educated women is primarily driven by a larger proportion of those with two children who go on to have a third child. This result suggests the emergence of a three-child norm among college-educated women.

These findings also suggest that the increase in TFRs among college-educated women had little to do with changes in fertility timing. "College-educated women tend to postpone their first births, but space higher-order births closer together, whereas those without a college degree, who generally have an earlier first birth, allow more time between pregnancies. However, over time, college-educated women are further postponing a first birth and also slightly increasing the spacing of higher-order births." says Zang.

"This is the first study to use the complete data of the whole generation to systematically demonstrate and analyze the educational differences in fertility levels and timing among U.S. cohorts who were born after 1960, and contributes to the current debate on whether highly-educated Generation X women are less ambitious in balancing family and career, and tend to prioritize child-rearing, compared to their Baby Boomer counterparts," says Zang.

Story Source:
Materials provided by Yale University. www.sciencedaily.com
Journal Reference:
Emma Zang. Women's educational attainment and fertility among Generation X in the United States. Population Studies, 2019; 1 DOI: 10.1080/00324728.2019.1658799

TREATMENT FOR 'LOW T' COULD SOMEDAY COME FROM A SINGLE SKIN CELL

Researchers have successfully grown human, testosterone-producing cells in the lab, paving the way to someday treat low testosterone with personalized replacement cells.

In Proceedings from the *National Academy of Sciences*, scientists describe how they transformed stem cells into functioning Leydig cells -- the cells in the testes that produce the male sex hormone.

"Our study provides a way to generate possible transplantation materials for clinical therapies, as well as a path toward testing and developing new drugs," said Vassilios Papadopoulos, dean of the USC School of Pharmacy, who led the research.

Millions of men have low testosterone, or hypogonadism, which impacts mood, fertility, sexual function, obesity and bone density -- and testosterone replacement therapy is a multibillion-dollar industry. Testosterone tapers off naturally with age but can also decrease suddenly due infections like mumps, or cancer treatment during childhood.

Testosterone replacement therapy -- injected, taken orally or applied as a gel - reverses many of these symptoms.

"You feel better, you lose weight, erectile function returns," Papadopoulos said. "Men love testosterone."

However, treatment for "low T" is linked to side effects such as infertility, increased risk of prostate cancer and cardiovascular diseases. In addition, topical treatments can rub off on close contacts, inadvertently exposing others to the drug. A transplant of lab-grown testosterone-producing cells, perhaps injected into fatty tissue, could potentially bypass those side effects, researchers say.

Previous attempts to cultivate Leydig cells have come up short. In one study, the lab-grown cells produced cortisol, not testosterone, Papadopoulos said. Other experiments have involved stem cells from bone marrow or the umbilical cord; harvesting these cells is more labor-intensive and they do not multiply as well in the lab.

In Papadopoulos's experiment reported today, researchers started with stem cells called human-induced pluripotent stem cells, which come from human skin or blood and can be developed into any type of cell needed for treatment purposes.

On a hunch, Papadopoulos added human collagen to his soup of nutrients, genes and other ingredients needed to transform stem cells into Leydig cells. Collagen is a common growth matrix ingredient; previously, Papadopoulos used bovine or rat collagen, which are cheaper and mostly interchangeable with other forms of collagen, at least in early-stage experiments.

This time, the lab-grown Leydig cells produced testosterone - and the cells even looked the same as their naturally occurring counterparts under the microscope.

"It was none of the things we thought. We had tried different genes, chemicals, everything - nothing!" he said. "The human collagen was the secret sauce."

Next, Papadopoulos wants to test how well lab-grown Leydig cells function, and for how long, when they are transplanted into animal models of hypogonadism. He's also eager to compare Leydig cells cultivated from skin cells from men with and without hypogonadism, to better understand the condition.

In addition to Papadopoulos, the paper's other authors are Lu Li, Yuchange Li, Chantal Sottas, Martine Culty, Yiman Hu and Garett Cheung of USC; Jinjiang Fan of McGill University in Montreal; and Hector Chemes of Hospital de Ninos in Buenos Aires.

Story Source:
Materials provided by University of Southern California. www.sciencedaily.com

Journal Reference:
Lu Li, Yuchang Li, Chantal Sottas, Martine Culty, Jinjiang Fan, Yiman Hu, Garett Cheung, Héctor E. Chemes, and Vassilios Papadopoulos. Directing differentiation of human induced pluripotent stem cells toward androgen-producing Leydig cells rather than adrenal cells. PNAS, 2019 DOI: 10.1073/pnas.1908207116

CELLS REQUIRED FOR DEVELOPMENT OF A HEALTHY UTERUS

Knowledge of the biological processes involved in the development of the uterus is important for understanding uterine health and fertility. A research team led by investigators at Massachusetts General Hospital (MGH) has uncovered important insights on a type of cell that is critical for the formation of a functioning uterus.

These cells are defined by their expression of Misr2+, the receptor for Mullerian Inhibiting Substance (MIS), which is secreted by the testes of male embryos to prevent the maturation of structures that would give rise to female reproductive organs.

While it is not surprising that Misr2+ cells would play a role in inhibiting the formation of a uterus in males, researchers found that these cells also actively participate in the formation of the uterus in females. The findings are published in eLife.

"The fate of these reproductive gatekeeper cells in the female, in the absence of MIS, was unknown," says senior author David Pépin, PhD, an assistant molecular biologist at MGH and an assistant professor of Surgery at Harvard Medical School. "In this study, we found that in females the cells continued to express the receptor to MIS, past the period of sexual differentiation in mice, rats, and humans. Furthermore, we showed that in rodents, these cells retained sensitivity to MIS, even after birth."

Treating rodents with MIS during the first week after birth interfered with uterine development and led to infertility later in life. "The findings suggest that the period of response to sexual differentiation signals in mammals may not be as restricted as previously thought," says Pépin.

To uncover more details, the scientists analyzed cells in the uterus of newborn rodents following treatment with MIS, and discovered that certain key cell types that contribute to the uterus' endometrium (the lining) were absent. The investigators suspect that Misr2+ cells normally develop into these cell types but were blocked when exposed to MIS.

"In the absence of these cells, a large number of important signals are disrupted, leading to abnormal uterine development," says Hatice Duygu Saatcioglu, the first author of the study. "This period is so critical for the specification of the uterine layers, that exposure to MIS for just a few days after birth leads to irrecoverable infertility later in life, with adults having a thin uterus composed almost entirely of myometrium," says Saatcioglu.

Patricia K. Donahoe, MD, a coauthor and director of surgical research laboratories at MassGeneral Hospital for Children (MGHfC), herself a longtime investigator of MIS functions, notes that the results may provide a better understanding of infertility caused by problems with the uterus. "Finding cells marked by Misr2 allows further investigation of how these cells can contribute to uterine pathologies causing infertility."

Conversely, some of the study's findings related to MIS may also be relevant to men, including those with a rare disorder called persistent Mullerian duct syndrome in which tissues such as the uterus may be partially retained due to mutations in MIS or its receptor.

Story Source: *www.sciencedaily.com*
Materials provided by Massachusetts General Hospital.
Journal Reference:
Hatice Duygu Saatcioglu, Motohiro Kano, Heiko Horn, Lihua Zhang, Wesley Samore, Nicholas Nagykery, Marie-Charlotte Meinsohn, Minsuk Hyun, Rana Suliman, Joy Poulo, Jennifer Hsu, Caitlin Sacha, Dan Wang, Guangping Gao, Kasper Lage, Esther Oliva, Mary E Morris Sabatini, Patricia K Donahoe, David Pépin. Single-cell sequencing of neonatal uterus reveals an Misr2 endometrial progenitor indispensable for fertility. eLife, 2019; 8
DOI: 10.7554/eLife.46349

ISAR CALENDAR 2019/2020

APRIL

18-21 April
ISAR BEST PRACTICE BEST OUTCOME COURSE : MUMBAI
30th April LAST DATE FOR SUBMISSION OF APPLICATION FOR THE ISAR ASPIRE FELLOWHIP COURSE: MUMBAI

MAY

12 May : ISAR STAFF VACCINATION

25-26 May
ISAR EMBRYLOLOGY CONSENSUS: DELHI

JUNE

1-2 June: ISAR IFS ACE CONSENSUS: DELHI (Minimum Standards of Infertility Practice: A Consensus Statement)

JULY

25-28 July
ISAR BEST PRACTICE BEST OUTCOME COURSE MUMBAI

AUGUST

16-18 Aug
YUVA ISAR : AGRA
24 Aug
ENDROCRINE DISRUPTORS MASTERCLASS BHUBANESHWAR

SEPTEMBER

15 Sep INFECTIONS IN ART MASTERCLASS: DELHI

23-29 Sep: ISAR ADVANCED ART COURSE

27 Sep: ISAR SKILL CERTIFICATION : MUMBAI

OCTOBER

1-7 Oct
FOGSI ISAR IAGE Artoscopia - Hysteroscopia : CAIRO EGYPT

NOVEMBER

8-9 Nov
DEMYSTIFYING MALE INFERTILITY MASTERCLASS
21- 24 Nov
ISAR BEST PRACTICE BEST OUTCOME COURSE: MUMBAI
30th Nov-ERROS IN ART MASTERCLASS:BENGALURU
30 Nov-1 Dec EMBRYOLOGY ISAR : BENGALURU

DECEMBER

13-14 Dec
ISAR HYSTEROSCOPY MASTERCLASS : KANYAKUMARI
21- 22 Dec
ART PREGNANCIES-ARE THEY DIFFERENT : INDORE

JANUARY 2020

9-12 Jan
ISAR BEST PRACTICE BEST OUTCOME COURSE : MUMBAI
18-19 Jan
STEM CELLS-THE NEW FRONTIER MASTERCLASS : PUSHKAR

FEBRUARY 2020

1-2 Feb 2020
ISAR IFS ACE CONSENSUS (Minimum Standards of Infertility Practice: A Consensus Statement)

MARCH 2020

6-8 March
ISAR SILVER JUBILEE CONFERENCE: HYDERABAD

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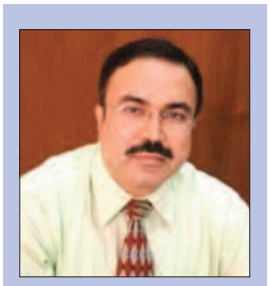
isar 2019
Towards Better Practices, Better Outcomes.

MYTHS & CONTROVERSIES

CLINICAL ART

AFFORDABLE ART FOR THE MASSES



DR GAUTAM KHASTGIR
MD, FRCS, FRCOG, FICOG
Medical Director,
BIRTH
Subspecialist in Reproductive Medicine & Surgery

Assisted Reproductive Technology (ART) has revolutionized the management of couples with the problem of infertility. It has been available over the last four decades and more than 5 million babies have been born with this treatment. However, the majority of infertile couples, especially in the developing countries like India, are unable to avail such facilities.

The disparity between the demand and supply of ART is largely due to its high cost. Affordability of ART is the biggest hurdle – the main barrier in accessing treatment. Since the success rate of ART is low, repetitive attempts may be necessary to achieve a favourable treatment outcome. That escalates the cost of treatment even further and thereby majority of patients drop out after one or two attempts. Although financial burden is the main cause for ART drop out, the other reasons for not continuing with the treatment are stress, agony, physical distress, uncertainty towards outcome and loss of time.

The main strategies for cost reduction of ART are follows: 1) careful patient selection, 2) simplifying pre-treatment investigations, 3) reduction in the cost of medicine, 4) streamlining clinical and laboratory steps of treatment, 5) better usage of laboratory facilities, 6) minimizing complications of treatment, and 7) arrangement of public healthcare funds.

The selection of ART over conventional therapy is mandatory in the following cases: 1) infertile women over the age of 38 years, 2) problem of more than 5 years duration, 3) associated tubal factor, 4) advanced endometriosis, and 5) severe male factor. Fertility experts must keep in mind that conventional therapies are safer, less stressful and more affordable, but it has a lower success rate and are of no benefit in certain situations. Moreover, when early results are desirable, ART is much more cost effective than conventional therapies. Primary ART without IUI is certainly more beneficial in patients with mild male factor and unexplained infertility.

The efficacy of treatment in those women who were supposed to have IUI but converted to ART due to hyper response to ovulation induction, has suggested that mild ovarian stimulation may be sufficient in the majority of patients. Such treatment regimen with clomiphene along with small dosage of gonadotrophins plays an important role in optimization of cost effectiveness for ART. In mild ovarian stimulation protocols the oocyte yield may be lower but of better quality. There is a minimum interference to the natural selection process of good quality oocytes and lesser exposer to potentially negative effects of ovarian stimulation agents, thereby resulting in a higher proportion of euploid embryos. In addition, due to relatively lower levels of oestradiol, the problem of embryo-endometrial asynchrony may be avoided. Although, development of fewer embryos and lower pregnancy rate has been reported, the cumulative pregnancy and live birth rates remain similar to standard ART.Mild ovarian stimulation can also reduce the incidence of OHSS which often discourages patients to come back for further treatment attempts. In modern ART protocol, the usage of antagonist, GnRH agonist trigger and freeze all embryo policy can defiantly eliminate OHSS for sure.

The efficacy and benefits of elective single embryo transfer (eSET) during ART are now well established. The cumulative success rates are comparable to multiple embryo transfers with a remarkably lower incidence of multiple pregnancy and its associated complications.Multiple pregnancies have to be avoided at all cost as it is associated with a higher incidence of preterm birth, low birth weight, handicapped child and cerebral palsy. Such complications are higher even in ART singleton pregnancies as in many cases,they start off as a twin pregnancy and become singleton with miscarriage of oneembryo in early pregnancy. Hence, there is a linear relationship between the number of embryo transferred and first trimester blood loss, which is commonly associated with poor pregnancy and neonatal outcome.

It is important to provide adequate information and counselling regarding a realistic success rate of ART in each individual patient. ART success depends on following parameters: 1) age and BMI of female partner, 2) duration of infertility, 3) any previous pregnancies, 4) baseline FSH, AMH and AFC values, 5) cause of infertility, 6) number of embryos transferred, 7) quality and day of embryo transfer, 8) exclusion of anuploidy embryos, 9) endometrial thickness and appearance, and 10) subendometrial blood flow. Thus each couple should be counselled about their individual ART-success rate and the need for repeating ART treatment up to six attempts.

In order to increase the acceptance of ART the clinicians must work hard to remove the prevail-

ing myths and misconceptions among general population. Even today the general belief is that ART is only for the rich and famous. Most infertile couples try to avoid ART as the last resort without realising that an early treatment would improve the success rate tremendously. People wrongly believe that the treatment is painful and requires prolonged bed rest which has to be continued throughout pregnancy. To add to this ever-increasing list of negatives is the opinion that ART babies are born with birth defects and would need special care throughout their lives.

It is therefore desirable to remove the misconceptions about untoward side effects of ART. The practice of mild ovarian stimulation and eSET can avoid the majority of side effects of ART that are related to multiple pregnancies and OHSS. Congenital anomalies in babies following ART are not caused by the treatment itself but largely due to associated parental factors. The majority of these patients are elderly, obese, hypertensive, diabetic along with their poor egg and sperm qualities. This is supported by the fact that there is no increase in birth defects in low risk patients with a singleton pregnancy following ART.

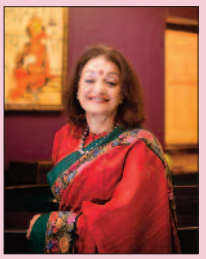
With the availability of universal public funding for ART, there is an increase in acceptability which confirms that it is the financial burden and not misconceptions or poor expectations that deter couples to avail treatment.With such financial help even clinicians change their approach to ART using milder ovarian stimulations and eSET. This automatically results in lower OHSS and fewer multiple pregnancies. The clinical pregnancy rate is lower but the cumulative success rate is much better with the option of repeating treatment cycles without any cost burden. It is interesting to note that the medical cost per cycle is lower resulting in lesser cost per live birth. The savings of fund with the changed approach can thereby pay for extra 55% ART cycles. However, the total cost of repeated ART cycles for many more patients availing treatment in the community would definitely be much higher.

Therefore, ART can only be offered to masses by changing the mindset of personals involved (both doctors and patients) along with an altered protocol for treatment. Individualised minimum ovarian stimulation is the most important step towards success and safety of ART. Proper case selection and counselling for a realistic expectation are essential to make ART acceptable. Outcome of treatment should be considered only on the basis of cumulative outcome of up to six ART attempts. For better results, ART should not be delayed as the last option of treatment for infertile couples. Finally, many low profit private and public funded ART centres are needed to reduce the cost burden of ART for people of low socioeconomic status which forms the majority of population in a developing country like India.

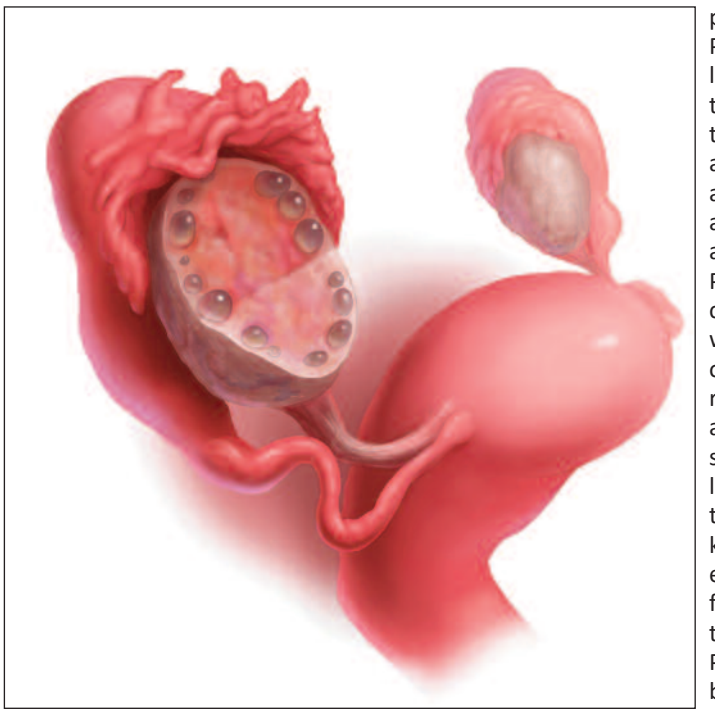
MYTHS & CONTROVERSIES

CLINICAL ART

CONTROVERSIES IN PCOS MANAGEMENT



PROF. DURU SHAH
MD,FRCOG, FCPS, FICS, FICOG, FICMCH, DGO,DFP



PCOS: A closely-knit web of multiple factors, a complex yet commonly encountered syndrome. A subject that has always joined hands with a number of controversies in its various aspects. Since the time it was first discovered 50 years back by Stein &Leventhal, numerous criteriae and theories have been established over the years. There is still a persistent need for detailed studies to unravel the mysteries of PCOS.

THE ORIGIN OF PCOS: Numerous theories have been cited to be the cause of PCOS, but no theory is yet definitive. These include the intrauterine, genetic, inflammatory, gut microbiota, insulin resistance and the kisspeptin theories.

Most recent theory is the Intrauterine theory which suggests that high maternal testosterone levels reprogramme the female reproductive axis to induce PCOS in later life.[1]

On the other hand, some studies show that genetically PCOS has an X-linked dominant mode of inheritance. Described as a polygenic pathology, there are several genes related to androgen and insulin metabolism, which are involved in PCOS.[2] An Association has also been established between pro-inflammatory genotypes and PCOS, involving TNF-alfa and Interleukins. Dysfunctional secretion of these genotypes may thus be related to abnormal ovulation, luteinization and even hyperandrogenism.2Weare all well aware of the fact that PCOS has always been linked with insulin resistance. (IR) is prevalent in women with PCOS independently of obesity. A recent study has shown that in PCOS women, physiologic hyperinsulinaemia of adolescence may be another factor responsible for it.2Certainintraovarian and extraovarian factors have been shown to compromise normal follicular development. The newest kid on the block is the discovery of kisspeptins. A hypothalamic peptide encoded by the KISS1 gene, has been found to be a key factor in the regulation of LH and FSH secretion, causing PCOS.[3] Women with PCOS had lower biodiversity in gut microbiota, and this was related with insulin resistance and abnormal lipid metabolism. Newer studies suggest that changes in the gut microbiome may influence the development and pathology of PCOS and its metabolic disorders as well.[4]

Thus the involvement of multiple factors gives rise to unending controversies to the etiology of PCOS. It is definitely a complex interplay of various factors, which affects women beyond their fertility.

THE DIAGNOSIS OF PCOS:

Next, the controversy stems over the proper diagnosis of the syndrome. The first guideline was put forward by the NIHCD in 1990. According to NIH criteria, a woman has to present with chronic oligoanovulation and either biochemical or clinical signs of hyperandrogenism. The guideline was later expanded according to the Rotterdam criteria (2003), set by both ESHRE & ASRM societies. This includes: chronic oligoanovulation/hyperandrogenism and polycystic ovaries on ultrasonography. (follicles>12 and volume>10cm3). Another set of criteria was put forward by the AEPCOS(2006), which stated that to diagnose PCOS, 2 out of 3 above criteria should be present, after exclusion of other causes of

Criteria for Diagnosis of PCOS

CLINICAL FINDING	NATIONAL INSTITUTES OF HEALTH CRITERIA, 1990 (MUST HAVE BOTH OF THE FINDINGS MARKED BELOW)	ROTTERDAM CRITERIA, 2003 (MUST HAVE ANY TWO OF THE FINDINGS MARKED BELOW)	ANDROGEN EXCESS AND PCOS SOCIETY, 2009 (MUST HAVE A PLUS EITHER B OR C)
Hyperandrogenism*	X	X	A
Oligomenorrhea	X	X	B
Polycystic ovaries		X	C

anovulation and hyperandrogenism. Recent re-evaluation of AEPCOS guidelines (2014) has suggested follicle number per ovary (FNPO) as >25 and ovarian volume > 10 as the new thresholds for diagnosing PCOS.[5]

Thus appropriate diagnostic cut-offs keep changing with time.Also, ultrasonographic evidence of polycystic ovaries as a diagnostic marker has substantially broadened the phenotypic spectrum of PCOS, yet much debate accompanies these newly identified variants of the syndrome. Clinical signs of hyperandrogenism are ill-defined in women with PCOS, and the diagnosis of hirsutism is largely subjective.We definitely need more confirmatory, age-specific thresholds for better diagnosis.[6]

THE MANAGEMENT OF PCOS:

Considerable controversy hovers around the management of PCOS. Thankfully, evidence based recommendations have now become available for better understanding of the subject.

Lifestyle interventions are undoubtedly the first line of non-pharmacological treatments recommended for PCOS.As PCOS can occur irrespective of the BMI, it has been found in 75% of lean and 95% of overweight women.7There has been much ado regarding the ideal dietary pattern for PCOS. With new diet fads including the keto diet, the mediterrean diet, the no gluten-no carb diet etc, controversy revolves around which one suits whom? A low calorie, low-carb diet, well distributed in portions and nutrients works well for pcos patients.[8] Exercise includes a combination of vigorous and moderate intensity workout coupled with resistance training activities.[9]

PHARMACOLOGICAL TREATMENT:

Coming to pharmacological treatment in PCOS, various controversies have been linked to a number of interventions. Use of oral contraceptive pills in PCOS alone or in combination with other agents has always been a topic of debate. COCP alone should be recommended in adult and adolescent PCOS women for management of oligo-anovulation and hyperandrogenism. WHO recommends OCP'swith 35 gms of EE and cyproterone acetate should only be used when treating moderate to severe hirsutism or acne due to higher DVT risk associated with it. For contraception, irregular menstrual cycles and mild hirsutism, other lower risk preparations are recommended first line.[10]

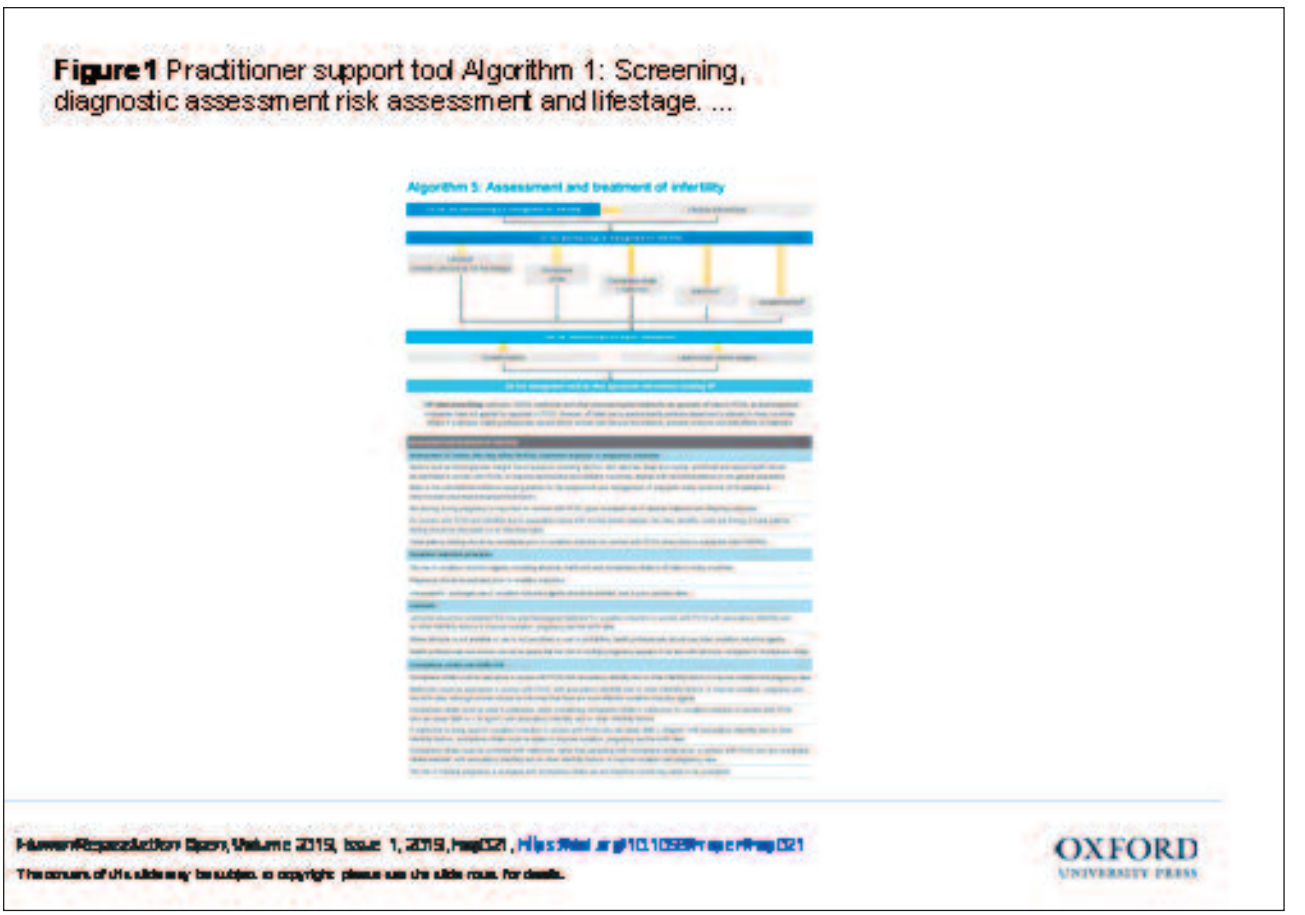
Evidence says that combined metformin and COCP offers additional benefits, but these do not exceed to the impact of COCP plus lifestyle changes.[11] Metformin is to be considered for obese as well as non-obese womenfor better weight, hormonal and metabolic outcomes.[11] Studies have shown that metformin works wonderfully well with women whose BMI is >25.Adjunct metformin during an IVF cycle helps improve clinical pregnancy rates and also decreases the risk of OHSS. Still the controversy lingers around its ideal therapeutic regimens and dosage.[12] There has also been much dispute regarding Vitamin B12 deficiency associated with the long-term use of metformin.[13] However, data from other populations suggests that adverse effects of metformin can be minimised with lower metformin starting dose or sustained release preparations.[14] As of now, we are unable to draw conclusions regarding the efficacy of other insulin-sensitising drugs.[15]

The role of Anti-obesity drugs is still unclear in PCOS due to its known side effects.11A regulatory status clearly needs to be established for these class of drugs.

Bariatric surgery improves weight loss and can improve comorbidities associated with PCOS. But as of now, its role and its effectiveness with other fertility therapies is yet to be established.

Definitive use of anti-androgen drugs in PCOS is again a hot debatable topic. If OCP'S are poorly tolerated, anti-androgens can be considered in the presence of an effective contraception.[16] Specific types or doses of antiandrogens cannot currently be recommended due to inadequate evidence.[16]

Inositols have been controversial since they were first reported to help in PCOS patients. Though ovulation rates appeared better with inositol, according to a recent study[17], its



use in any form is still considered an experimental therapy in PCOS.[11] The precise mechanisms through which inositols (MI & DCI) ameliorate insulin resistance is still poorly understood. Studies show that the synergistic combination of both MI & DCI works better, but the ideal ratio to be used is still controversial. Most available preparations provide very low amounts of DCI, which is insufficient for PCOS.[18] In case of fertility-desiring patients, the primary concern is to restore regular ovulatory cycles. As per recommendations, aromatase inhibitors like Letrozole have been advised as the first line agent in PCOS patients.Upon meta-analysis, we found that letrozole was better than CC for ovulation, pregnancy and live birth rate per patient. It also gives lower multiple pregnancy rates and less abortion rates in CC resistant PCOS patients.[19] Though the adverse effects and the overall effect of letrozole has always remained controversial, recent meta-analysis failed to find any increased rate of congenital anomaly with its use.[20] Clomiphene citrate is now recommended as the second line agent for ovulation induction. First approved for use in 1967, recent studyshowed that metformin was as good as CC in terms of "LBR" and the combination of CC and metformin gave the highest ovulation and LBR.[21] There is still a controversy to determine whether CC or gonadotropin is superior. There is compelling evidence for the superiority of letrozole over CC with a 40% increase in pregnancy rates and a shorter time-to-pregnancy.[22] There is still no ideal regimen established for the dose of CC. A recent study advocated the stair-step up protocol for ovulation induction, but more conclusive studies are needed.[23] Gonadotropins have been considered as the second-line therapy for PCOS patients when other first-line agents have failed. Controversies have risen regarding the use of gonadotropins alone or with letrozole, CC or CC with metformin. Gonadotrophins, where available and affordable, should be used in preference to clomiphene citrate + metformin therapy in women with anovulatory PCOS, clomiphene citrate-resistance and no other infertility factors.[24] The dose, the protocol and the type of gonadotropin to be used has always been a matter of great debate. A chronic, low dose step-up protocol or a step down protocol is the preferred choice than the standard regimen in PCOS patients. Though there is much controversy around the type of gonadotropin to be used, both urinary and recombinant gonadotropins have given similar live birth rates. The choice of the gonadotropin depends on the availability, convenience and costs. Also, an antagonist protocol is the preferred protocol as it reduces the duration/dose of stimulation and of course the risk of OHSS.No statistically significant differences were found be-

tween both agonist and antagonist protocol.[24]

THE TRIGGER:

Clarification regarding the choice of trigger is yet another controversy. The choice to trigger final oocyte maturation with GnRH-agonist instead of hCG is important in order to prevent OHSS. GnRH- agonist triggers are associated with lower pregnancy rates, primarily in fresh embryo transfers, which can be overcome in frozen cycles. The recent concept of dual trigger (low dose hcg and 0.1mg triptorelin) leads to better number and maturity of eggs.[25]

There is insufficient evidence to determine the benefits of using or not using exogenous LH for better fertility outcomes. Though LH is essential for final oocyte maturation, PCOS patients with a high FSH/LH ratio can have deleterious effects with initial follicular use of LH.

IVM (In-vitro-maturation of oocytes), is it really effective in PCOS patients? The absence of any RCT rakes up yet another controversy regarding the use of IVM. Although retrospective studies suggest that IVM is better in a fresh embryo transfer cycle, there are also studies which talk about the higher risk of embryo arrest in IVM.[26] Observational studies suggest that offspring from IVM are not adversely affected.[27]

Controversy regarding laparoscopic ovarian drilling is never ending. The risks of lowered ovarian reserve and peritubal adhesions is a downside to LOD. It is recommended as a second line therapy for those who are CC resistant and with no other infertility factors. Recent studies show that unilateral drilling is better than bilateral drilling in CC resistant PCOS.[28] There are RCT's regarding the use of LOD vs CC/letrozole which have found no difference between both the interventions.[11]

CONCLUSION:

Polycystic ovary syndrome remains a highly controversial topic because of its undetermined and largely variable etiology. We believe a conservative diagnosis and long-term follow-up of PCOS patients will go a long way in management of these patients. It is difficult to accept any other criteria otherthan the Rotterdam criteria for diagnosis as of now, because these criteria permit all the investigations of PCOS-related features and all the possible phenotypic combinations. Improving the accuracy and reliability of our methods for evaluating features of PCOS still remains. All our attempts at early diagnosis and management in PCOS will always be an obstacle if these controversies remain ignored.

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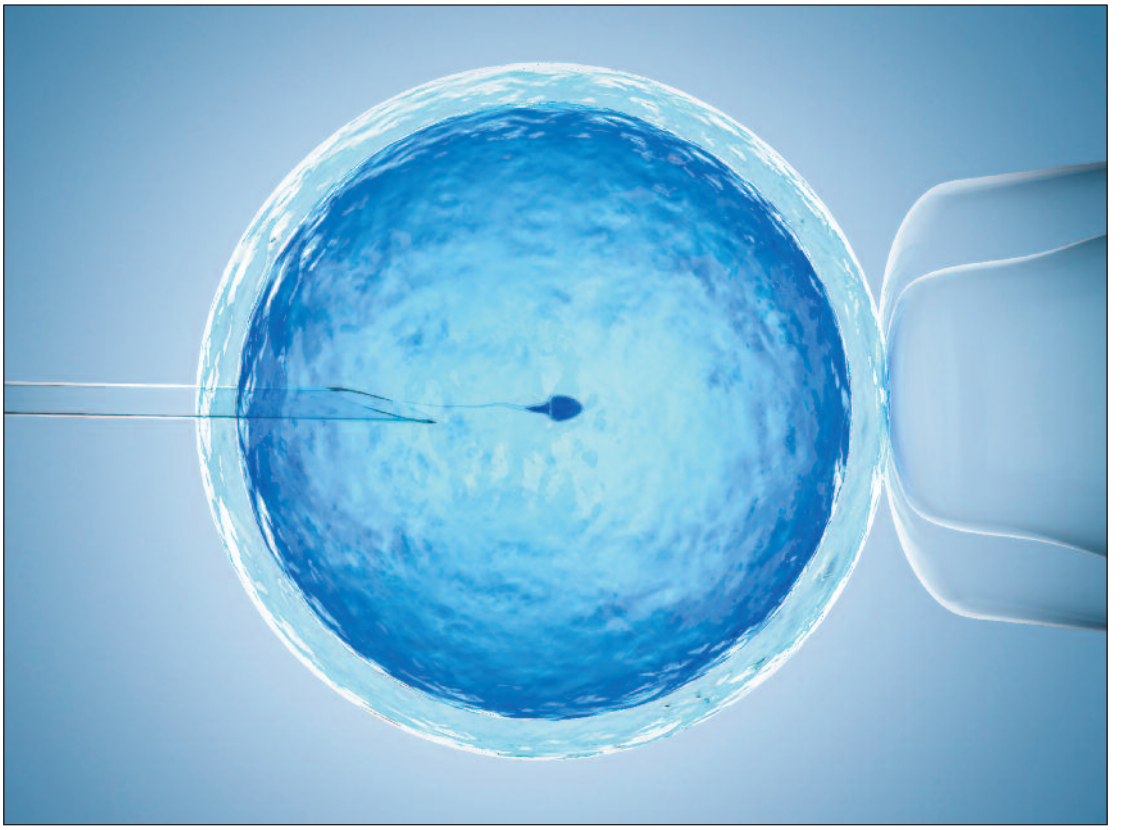
MYTHS & CONTROVERSIES

CLINICAL ART

DR SAGARIKA BASU
MBBS, DFFP (UK), MRCOG (London), CCT (UK)
Consultant - Gynaecology and Infertility

CONTROVERSIES IN ICSI FOR ALL VERSUS MALE INFERTILITY ONLY



INTRODUCTION

Assisted reproductive treatment has made a significant advancement over the last four decades. Up until 2018, an estimated 8 million births have happened since the first In Vitro Fertilisation (IVF) conceived baby was born in 1978 [1].The 1980s were marked by major improvements in "traditional IVF" procedure. 1990s witnessed the emergence of Intra Cytoplasmic Sperm Injection (ICSI) that helped women to conceive who had otherwise failed to do so in conventional assisted reproductive technologies [2]. And the newest addition in the millennium has been vitrification and genetic testing. Over the time ICSI has gained its popularity. It has been reported that ICSI consists of 66% of IVF cycles in USA [3]. ICSI is now used in two thirds of fresh ART cycles with an ICSI:IVF ratio of 4:1 in Asia and 80-100% ICSI cycles in the Middle East[4]. There is ever increasing concern about its expanding use and safety over last two decades.

WHAT IS ICSI?

Intra-cytoplasmic sperm injection (ICSI) is a breakthrough technique in IVF treatment that has changed the perspective of treatment of infertile couples. Controlled ovarian stimulation is done with Gonadotrophin Releasing Hormone agonist (GnRHa) protocol or GnRH antagonist protocol with recombinant or urinary Follicle Stimulating Hormone (FSH) or Human Menopausal Gonadotrophin (HMG) preparations. When at least 3 follicles reach a size of 18 mm, 10000 IU of Human Chorionic Gonadotrophin (HCG) is administered and oocyte retrieval is performed 35-36 hours after HCG trigger. In conventional IVF, the retrieved oocytes are inseminated 4 hours after insemination with 60,000 to 1,00,000 motile sperms in 1ml of medium. In ICSI, mature oocytes (M II) are selected, a single motile spermatozoa with apparently normal morphology is injected into the ooplasm at 3 o' clock position. Fertilisation is evaluated after 16-18 hours

after IVF or ICSI. Normal fertilisation is defined as presence zygotes with 2 pronuclei (PN). Zygotes with 2 PN are cultured and embryos are transferred after 48-72 hours. Luteal phase support is provided with progesterone. A positive serum HCG confirms chemical pregnancy 14 days after embryo transfer. An ultrasound scan is performed at 6-7 weeks gestation to identify foetal heart to confirm clinical pregnancy [5].

INDICATIONS FOR ICSI

Male factor infertility has been the primary indication for ICSI since its inception. That includes suboptimal semen quality with low sperm count, less motile sperm. It has also been effective in dysfunctional sperm defects. The use of ICSI with normal semen parameters has become more popular recently. Common indications for which it has been increasingly utilised are routine use in all IVF cycles, unexplained infertility, prior fertilisation failure with conventional IVF, poor quality oocytes, low oocyte yield, advanced maternal age, pre implantation genetic testing (PGT), fertilisation after in vitro maturation (IVM) and fertilisation of cryopreserved oocytes[6].

There is widespread use of ICSI routinely for all oocytes irrespective of the cause of infertility. The logic has been used that it reduces likelihood of failed fertilisation and will enhance the number of embryos [7,8]. Bhattacharya et al conducted a well-powered multi centre randomised controlled trial that compared outcomes following IVF and ICSI in 415 couples with non-male factor infertility. Fertilisation rate per retrieved oocyte was higher in IVF than ICSI (58% vs. 47%, P<0.001). Fertilisation failure occurred in 5% and 2% in IVF and ICSI respectively. Therefore, number needed to treat (NNT) with ICSI to prevent 1 case of fertilisation failure is 33. Similar pregnancy rate was reported in IVF and ICSI (33 % vs. 26%, RR 1.27 CI 0.95-1.72). This study suggested that ICSI should be reserved for couples with male factor infertility [9]. Other non-randomised studies have also supported this view [10-12].

Hershlag et al and Jaroudi et al studied traditional IVF and ICSI in patients with unexplained infertility using sibling oocytes. Fertilisation rates were higher in ICSI than IVF (65.3% vs 48.1%, P < 0.001 and 61% vs 51.6%, P < 0.001 respectively). Fertilisation failure was more common in IVF compared to ICSI; 0% vs 16.7%, P< 0.002 and 0.8% vs 19.2%, P < 0.00113, [14]. Foong et al looked at a group of 60 women with unexplained infertility and randomised them to conventional IVF and ICSI. There was no difference in primary outcome such as fertilisation rate (77.2% vs 82.4%) as well as secondary outcome i.e. embryo quality, implantation rate (38.2% vs 44.4%), clinical pregnancy rate (50% in each group) and live birth rate (46.7% vs50%)15.Another randomised trial with 100 women found similar results[16]. Overall, current evidence does not demonstrate any benefit of ICSI in couples with unexplained infertility.

In cases of total failed fertilisation with traditional IVF can be related to poor stimulation in IVF but utilising IVF/ICSI is associated with decrease in the rate of failed fertilisation [17].

It has always been a challenge to deal with cases with morphologically abnormal oocytes in presence of normal semen parameters. No studies have been identified which describe improvement in clinical outcome with ICSI in cases with poor quality oocytes.

In theory, ICSI can be used in cases of low oocyte count in order to achieve a higher number of embryos. ICSI provides comparable results with IVF in terms of fertilisation rate (77.7% vs. 70.2%), fertilisation failure (11.5% for each), mean embryos per patient (2.5% vs. 2.2%), clinical pregnancy rate (17.3% vs. 21.1%) and miscarriage rates (33.3% vs. 36.4%)[18,19].

It is commonly believed that oocytes from older women (advanced maternal age) have structural problems of zonapellucida and cytoplasm that may render fertilisation difficult with conventional IVF. Kim et al showed no difference in fertilisation of oocytes of women more than 35 years compared to younger women in ICSI and IVF[20]. There has not been any study assessing the benefits of ICSI in specific age group in terms of embryo quality and implantation rate.

ICSI can be an option in cases where pre-implantation genetic test (PGT) is required for embryo. The reasoning behind this is to ensure monospermic fertilisation and therefore it obviates thepotential paternal contamination from extraneous spermatozoa attached to zonapellucida. [21,22]. Although there is no randomised controlled trial to support this but the concerns of inaccurate results from extraneous sperm contamination justifies the use of ICSI in cases of PGT.

In vitro maturation (IVM) may lead to alteration in zonapellucida that in turn may result in reduced fertilisation with IVF[23,24]. Fertilisation rate of 37.7% following IVF versus 69.3% with ICSI following metaphase II (M II) oocytes have been reported. Pregnancy rates are similar between IVF and ICSI (23.8% vs. 17.1%) whereas implantation rate from oocytes from IVF are higher than ICSI (24.2% vs 14.8%, P <0.05) 7.

ICSI is the preferred method of fertilising cryopreserved oocytes. Freezing oocytes involves removal of cumulus cells that leads to alteration of zona and in turn potential of reduced fertilisation with conventional IVF[25].

> A considerable proportion of men requiring ICSI have low sperm counts associated with chromosomal abnormalities. ICSI is dependant on selection of spermatozoa based on motility and morphology measures. Spermatozoa with normal morphology may have DNA fragmentation and can be mistakenly selected to fertilise oocyte in ICSI. Sperm DNA damage can give rise to mutations after fertilisation, as the oocyte attempts to repair the damage prior to the first cleavage.

HOW SAFE IS ICSI?

There has been a significant increase in the number of children born by ICSI and consequently there has been an increasing focus on the safety of this procedure. It is important to consider the im-

mediate effects as well as the long-term implications.
The potential risks of ICSI focus on four general areas. These are transmission of congenital malformations, genetic anomalies, developmental abnormalities and imprinting disorders. Hansen et al. first described the association of congenital malformations and ART, where a twofold increase in major birth defects were observed in children born by ART. Musculoskeletal, cardiovascular and urogenital malformations are the commonest malformations [26]. There is a 4.2% risk of major malformations in IVF/ICSI cycles as stated by American Society of Reproductive Medicine (ASRM) [27,28]. Previous studies have not shown significant difference between IVF & ICSI[26,27]. However, Davies et al. 2012 has suggested that ICSI may be involved with higher chance of congenital malformations [29].

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Several studies have not found any significant difference in long term developmental outcome of ICSI offspring. There is reassuring information regarding physical growth of ICSI children upto the age of 12 years [33]. Another study has not shown any significant difference in neurodevelopmental outcome with a follow up until the age of 5.5 years [32].
In ICSI there is an increasing incidence of epigenetic abnormalities. Genetic imprinting involves selection of specific genes from a single parent. Imprinting disorders occur when this imprint is not set correctly. Altered gene expression of imprinted genes occurs during gamete micro-manipulation and crucial epigenetic reprogramming happens during germ cell development and early embryogenesis34. Suboptimal culture conditions affect gene expression and foetal development[34,35].
Beckwith Weidemann Syndrome and Angelman Syndrome are two such examples of imprinting disorders.
It is difficult to understand whether the birth defects associated with ART are due to any particular type of ART or due to the underlying maternal/paternal factors that necessitate ART. Davies et al. suggested that the risk of any birth defect (when confounding factors were taken into account) with ART is 8.3% as compared to 5.8% in naturally conceived pregnancy. On independentanalysis of the ART methods, the risk of birth defects in ICSI is 9.9% compared to 7.2% in IVF[29]. This is somewhat reassuring to couples undertaking IVF, that there is risk of having an offspring with a birth defect is not increased beyond their biological risk. However, this can also be interpreted as couples having ICSI have 77% higher chance of having a child with birth defect compared to 26% in IVF. Moreover, when the confounders are considered, this risk comes down to 7% in IVF while it stays at 57% in ICSI. After multivariate adjustment, the risk in IVF is not significant whereas that in ICSI remains significant [29]. ICSI may be playing a role in transferring genetic abnormalities to the future generation by avoiding the natural process of sperm selection. Currently the most common method of measuring DNA fragmentation is sperm chromatin structure assay (SCSA). It is a test to determine the percentage of sperm with a high susceptibility of undergoing DNA fragmentation and is expressed as DNA fragmentation index (%DFI)[36,37]. Generally levels more than 30% DFI cannot achieve an on-going pregnancy. Newer methods like TUNEL and Comet assays measure both single and double strand DNA breaks but are not incorporated in clinical practice. It is important to discuss the results of a Swedish study of 15, 570 ART infants, which demonstrated that the adjusted odds ratio for birth defects in ICSI versus IVF was 0.90 (95% CI 0.78-1.04)[38]. There was no risk difference based on the method of ART. A recent meta-analysis of 46 studies involving 125,000 ART babies showed a small increase in the risk of birth defect in IVF and ICSI babies compared to natural conception, but no difference in risk between IVF and ICSI (RR=1.05, 95% CI 0.91-1.20)[39].

DISCUSSION

In one hand, ICSI has proved to be a ray of hope to couples with severe male factor infertility where IVF did not play much role. On the other hand, it has hampered the development of diagnostic tools and medical treatment of male infertility. Many couples are diagnosed with so called unexplained infertility and most men do not receive any explanation for their reduced semen quality. It is also important to realise that ICSI would incur about 11% additional cost compared to standard IVF cycle. That might have played a role in its increasing popularity amongst infertility clinics[40-42].ICSI offers no benefit over conventional IVF without male factor indication according to a large multi centre study[43]. A large population based study involving almost 5000 patients in Belgium and Spain has not shown any benefit in terms of fresh and cumulative live birth rate in patients treated by ICSI compared to IVF for non male factor infertility. The result of this study was presented in the Annual Meeting of ESHRE 2019. Along with comparing out-

come in ICSI and IVF in non-male factor infertility, this study also compared outcomes in different types of patient response to ovarian stimulation. ICSI is gaining popularity over IVF worldwide. The rationale behind this seems to be an increased likelihood of fertilisation and increased number of embryos in ICSI cycle. However this is controversial. Also ICSI is the choice of ART in patients who have a mild response to ovarian stimulation and have fewer eggs retrieved. However there is so far no evidence of effectiveness of ICSI based on the number of eggs retrieved in patients with non-male factor infertility. This study showed no difference in outcomes like fertilisation rate, live birth rate and cumulative live birth rate in ICSI or IVF cycles. These comparable findings were evident in different patient response groups ranging from poor responders to high responders. According to both global European registries, 70% of all cases were ICSI in 2015. Pregnancy rates were slightly higher in IVF than ICSI (27.7% versus 25.5%). High rates of ICSI were seen in Eastern and Mediterranean Europe. A 50:50 split between ICSI and IVF were seen in some Nordic countries, UK and France. The most recent HFEA report suggested a steady rise in ICSI rate till 2014 but now in decline possibly due to a consensus in opinion that it is not required in all indications. This studydescribed the data to be sufficiently robust to convince the clinicians to judiciously apply ICSI for infertile couples with male factor and also emphasised on the cost implication of ICSI on patients.

CONCLUSION

Although there has been no evidence showing benefit of ICSI over IVF in terms of clinical outcome, there has been a steady increase in the utilisation of ICSI over conventional IVF in couples with non male factor infertility throughout the globe. Widespread research is desperately required before firm conclusions can be drawn about long-term safety of ICSI. There is potential of epigenetic modifications induced by ICSI procedure; the effects of these will not be apparent till later life and requires a longer follow up. Studies focusing on neurodevelopment during infancy and childhood have shown reassuring results; whereas those studies which evaluated neurodevelopmental disorders, growth, general physical health and childhood cancer are inconclusive. Studies assessing different health issues in specific age groups like adolescent and adults are required. Underlying paternal infertility can contribute as can the ICSI procedure itself play a role in any adverse health effect of the offspring. It is imperative to conduct studies that can differentiate between the two. If ICSI is deemed to be the suitable method of ART, the associated concerns of birth defects should be discussed with the couple in details.

Hopefully future research will be able to balance improvements in conception rate and minimise chances of birth defects in pregnancies resulting from ICSI. Till then ICSI is better reserved for its initial indication for couples with male factor infertility.

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CONTROVERSY OF FRESH VERSUS FROZEN EMBRYO TRANSFER IN IVF

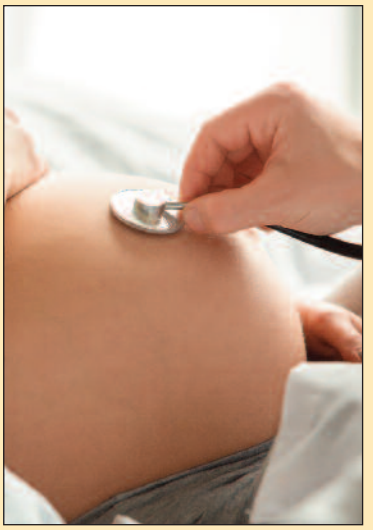
DR AINDRI SANYAL
MBBS, MD - Obstetrics & Gynaecology, FNB - Reproductive Medicine
Clinical Director, Motherhood Fertility, Kolkata

Since the birth of the first infant conceived by frozen thawed embryo transfer in 1984, the proportion of thawed embryo transfer has increased significantly,not only because of the refinement of laboratory techniques,but also because protocols of frozen thawed embryo transfer are simpler than fresh transfer.In frozen thawed embryo transfer cycles,the main aim is to prepare suitable endometrium, giving time to the ovary to recover from controlled ovarian stimulation, avoiding embryo transfer into an adverse endocrinologic profile or endometrial cavity. Though shifting fresh embryo transfer to frozen embryo transfer is becoming more common in many programs,yet some still disagree how to choose a transfer programme (fresh versus frozen) and the safety of mothers and infants after transfer is also a matter of concern.

Multiple studies compared the obstetric and perinatal outcomes, but the results were controversial. A Catalan cohort study showed that infants born after frozen embryo transfer were likely to get a higher birth weight and a higher risk of being large for gestational age (LGA). Luke et al also drew the same conclusions (Luke B et al.Increased risk of large for gestational age birth weight in singleton siblings conceived with in vitro fertilization in frozen versus fresh cycles. J. AssiReprd Genet 2017)

Some clinical experiments concluded that frozen thawed and fresh tranfers had similar possibilities of pregnacy and perinatal outome. (Wikland M et al.Obstetric outcomes after transfer of vitrified blastocysts.HumReprod 2010)

In addition some meta analysis proved that frozen thawed embryo transfer had a better perinatal outcome than fresh in In VitroFertilization /Intracytoplas-



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mic Sperm Injection Transfer (Zhao J, Which one has better obstetric and perinatal outcome,IVF/ICSI or FET? a systematic review and meta-analysis. Hum Reprod 2010)

A meta analysis of four randomized clinical trials however demonstrated that the freeze all strategy had a higher rate of pregnancy complications and no difference in cumulative live birth rates than IVF/ICSI strategy.

An interesting meta analysis compared the differences between fresh and frozen embryo transfers in Asian populations found that a frozen embryo transfer could decrease the risks of ectopic gestation, premature delivery, SGA, VLBW, placental abruption and stillbirth over those with a fresh transfer strategy, whereas a fresh embryo transfer strategy could decrease the risks of LGA, PIH and placenta accrete over those with a frozen embryo strategy in Asian people. Therefore frozen embryo transfer is a better choice for most Asians (YezhouSu et al.Differences between fresh embryo transfer and frozen embryo transfer in Asian populations:a meta ananlysis.Int J Clin Exp Med 2018)

SO TO SUM UP... FREEZE ALL, THE STORY SO FAR...

1. The concept of freezing all embryos for deferred transfer was first raised as a safety measure for IVF patients responding excessively to ovarian stimulation. Because of the link between OHSS and hCG, it was thought that triggering ovulation with an alternative to hCG and avoiding pregnancy in the treatment cycle would minimize exposure to hCG and thereby lower the OHSS risk (Devroey P,PolyzosNP,BlockeelC.An OHSS free clinic by segmentation of IVF treatment.HumReprod 2011)

2. Since then, against a background claim that ovarian stimulation may also be detrimental to implantation, many clinics have adopted a freeze all strategy with the aim of not just of lowering the risk of OHSS but also of improving delivery rates in a later non stimulated drug free cycle.

3. So far, study results (trials and meta analyses) have been inconsistent with most showing no outcome benefit in patients with normal ovulatory cycles. The first and only big trail showing an improvement in outcome in a general IVF patient population came earlier this year from China (Wei D,Liu J-Y,Sun Y et al.Frozen versus fresh single blastocyst transfer in ovulatory women:amulticenter,randomized controlled trial.Lancet 2019)

A large randomized trial involving 460 patients at eight clinics of Denmark, Sweden and Spain presented at the ESHRE convention at Vienna in June 2019, has conclusively shown that the increasingly popular trend for fertility clinics to freeze all IVF embryos for later transfer, has been shown to offer no improvement in delivery rates over fresh embryo transfers. Results showed that the ongoing pregnancy rate per randomized patient after the first single blastocyst transfer was similar in the 2 groups, 26.1% in the freeze all group and 28.8% in the fresh transfer group, a statistically non significant difference, suggesting that a general freeze all policy will bring no patient benefit in terms of pregnancy outcome. Live birth rates were also comparable. The findings therefore gave no support to a general freeze all strategy in normally menstruating women.

So till the time the debate continues and we arrive at a relative consensus regarding fresh versus freeze all strategy, it would suffice to say, for the time being, the only logical situations for a mandatory freeze all strategy would be polycystic ovarian patients at risk of hyperstimulation following COH and patients undergoing PGT-A cycles for whatsoever indications. For the rest of the patients it has to be a carefully planned, strategized and customized approach to the question of embryo transfer.

MYTHS OF STEM CELL THERAPY IN INFERTILITY

DR ASHISH RAMCHANDRA KALE
MD, DNB, MNAMS, FICS, DEPS, MICOG
IVF consultant and founder director Ashakiran group of Hospitals and Asha IVF centre Pune

DR ASHWINI ASHISH KALE
DGO, DNB (OBGY)
IVF consultant and Embryologist Ashakiran Hospital and ASHA IVF centre Pune

DR NARENDRA MALHOTRA
MD, FICOG, FICMCH, FRCOG, FICS, FMAS, AFIAP
Managing Director GLOBAL RAINBOW HEALTH CARE, Agra Director ART-RAINBOW –IVF (Agra & Delhi)

INTRODUCTION

Stem cells are undifferentiated cells present in the embryonic, foetal and adults. Which is then converted to differentiated cells, that are building blocks of tissues and organs. Self-renewal, colonality, potency are the major characteristics of stem cells. These cells can be derived from amnion, chorion, placenta and umbilical cord (Volarevic et al., 2014).

STEM CELLS: MYTHS AND REALITIES

MYTH: Stem cells research is unethical.

REALITY: Stem cells research are taken seriously. They comply with comprehensive guidelines and regulations (cirm_2.0, 2009).

MYTH: The embryos for IVF are used for stem cell research

REALITY: The embryos that the couple have not chosen for the implant are used with the permission from the donor for the extraction of embryonic stem cells. The blastocysts for this research are developed in laboratory dishes in fertility clinics. These early stage embryos consist of about 100 cells. At this stage, the cells are undifferentiated: They have no nervous system, no heart, no limbs and no specialized human tissues. (cirm_2.0, 2009) ("University of Michigan Stem Cell Research | Frequently Asked Questions," 2013.).

MYTH: Embryonic stem cells come from aborted foetuses.

REALITY: Embryonic stem cells come from a four to five-day old blastocyte. There is no connection be-

tween abortion and human embryonic stem cells. By the time a human embryo has been inserted in the uterus, its cells have specialized to the point where they can no longer be used for the derivation of embryonic stem cell lines (cirm_2.0, 2009) ("University of Michigan Stem Cell Research | Frequently Asked Questions," 2013.).

MYTH: Embryonic stem cell lines destroy the embryo.

REALITY: Embryonic stem cells do destroy the embryos in some cases during the extraction process. However, another method where one cell is removed at an early stage prevents it (cirm_2.0, 2009).

MYTH: Adult stem cells are good for therapies than embryonic stem cells.

REALITY: Adult stem cells have limited properties and follow certain path. Whereas, embryonic stem cells can grow to a desired cell type (cirm_2.0, 2009) ("University of Michigan Stem Cell Research | Frequently Asked Questions," 2013.).

MYTH: Stem cells from amniotic fluid and umbilical cord blood can be used instead of embryonic stem cells ("University of Michigan Stem Cell Research | Frequently Asked Questions,"2013.).

REALITY: Amniotic fluid and umbilical cord blood contain adult stem cells. They hold promise for therapy but do not have the properties or potential of embryonic stem cells ("University of Michigan Stem Cell Research | Frequently Asked Questions," 2013.).

MYTH: Embryos discarded by fertility clinics could be donated to another family rather than discarded or used for research.

REALITY: Many embryos created for IVF are discarded because they do not develop normally or are known to carry serious genetic abnormalities hence not suitable for implantation. Thus, these defective embryos can be used in research ("University of Michigan Stem Cell Research | Frequently Asked Questions," 2013.).

MYTH: Generation of gamete from pluripotent stem cells are beneficial for infertility

REALITY: Induced pluripotent stem cells (iPSCs) technology helps in reprogramming of a differentiated somatic cell into a pluripotent state. With the development of iPSCs, numerous studies generated primordial germ cell stage to mature gamete-like cells in vitro in mice and humans (Mouka et al., 2016). Next generation sequencing, gene editing and differentiation of germline cells from pluripotent stem cells has revealed that the core molecular mechanisms that regulate human germline development are different from rodents (Chen et al., 2017).

MYTH: Stem cell therapy is done only for females

REALITY: Spermatozoal stem cells are a potential tool for the treatment of male infertility due to their ability to differentiate into male gametes in vitro and capacity to restore male fertility in vivo. SSC are adult stem cells, but SSC-derived cells, called multipotent adult germline stem cells (maGSC), have differentiation potential (Volarevic et al., 2014).

MYTH: Autologous stem cell ovarian transplant is infective among poor responders to the therapy

REALITY: The Autologous stem cell ovarian tranplant optimized the mobilization and growth of existing follicles, possibly related to fibroblast growth factor-2 and thrombospondin-1 within apheresis. The ASCOT improved follicle and oocyte quantity enabling pregnancy in women who are poor responders previously limited to oocyte donation (Herraiz et al., 2018).

MYTH: Stem cell therapy cannot be performed with thin endometrium

REALITY: Stem cell therapy method is becoming a novel procedure for treatment of tissue injury and fibrosis in response to damage. There is consistent emerging evidence that there appears that stem cells are looked upon a novel treatment method for regenerative medicine including regeneration of human endometrium disorder like Asherman syndrome and thin endometrium. This is classically an intrauterine adhesion disorder wherein there is a uterine disorder with the aberrant creation of adhesions within the uterus and/or cervix. It is evident that the transplantation of different stem cells from diverse source in the endometrial zone had effects on endometrium which includes: (Azizi et al., 2018).

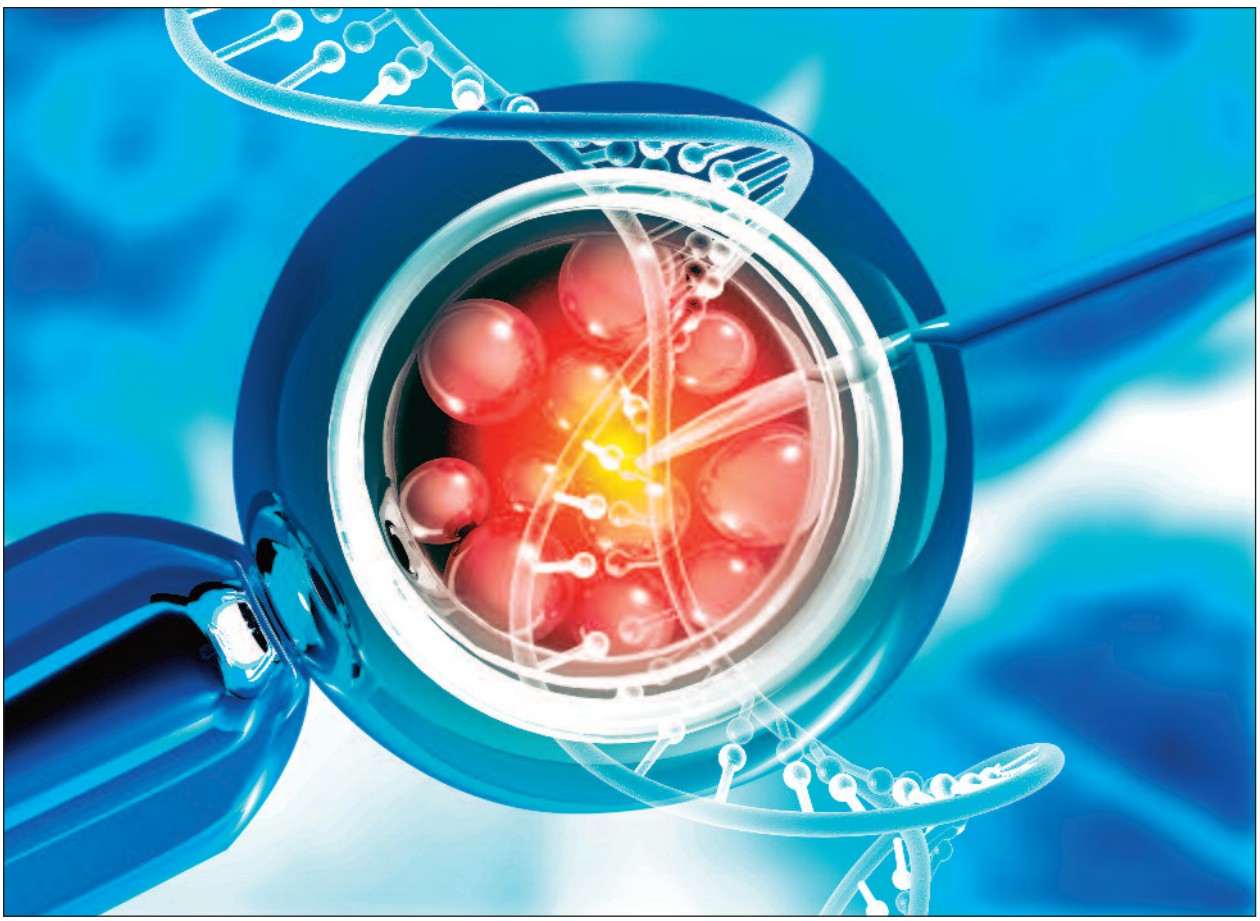
a. Declined the fibrotic area
b. Elevated number of glands
c. Stimulated angiogenesis
d. Enhanced thickness of the endometrium
e. Better formed tissue construction
f. Protected gestation, and
g. Culminating to the improved pregnancy rate

MYTH: Stem cell therapy isn't effective in women who have low anti-mullerian hormone (AMH)

REALITY: Very low AMH, is usually considered below 1.05 ng/ml, has been associated with extremely low pregnancy chances and many IVF centers flat out deny treatment to women with such low levels of AMH ("Anti-Müllerian Hormone (AMH) - Treatment for Low AMH Levels | CHR," 2018.). The Autologous Stem Cell Ovarian Transplantation led to a significant improvement in anti-follicular counts after treatment. With an increase anti-follicular and anti-mullerian hormone levels, improvement in the ovarian function is seen in 81.3% of women. These positive effects were associated with the presence of fibroblast growth factor-2 and thrombospondin (Herraiz et al., 2018) (Christianson and Segars, 2018).

MYTH: Stem cell therapy do not help restore fertility in female cancer survivors

REALITY: After the umbilical cord blood mesenchymal stem cell therapy in chemotherapy patients, the ovarian function was restored in the form of, a. Increase in ovarian weight and estrogen dependent organs, b. increase in fol-



licular counts, c. decrease in FSH serum levels, d. increase in anti-mullerian hormone levels (Mohamed et al., 2019). A 45 year old Indian woman from Pune delivered a healthy female baby weighing 2.7 kgs due to stem cell therapy and assisted reproduction (Gupta et al., 2018).

MYTH: Platelet rich plasma treatment has a therapeutic effect on intra uterine adhesion

REALITY: Menstrual blood stomal cells, effectively improved uterine proliferation, markedly accelerated endometrial damage repairment and promoted fertility restoration in IUA rats, suggesting a paracrine restorative effect and Hippo signaling pathway stimulation ("Platelet-rich plasma improves therapeutic effects of menstrual blood-derived stromal cells in rat model of intrauterine adhesion,"2019.).

MYTH: Platelet rich plasma and its effect on human ovaries

REALITY: Emerging evidence reflects utility end of future directions for the outcome of the results are guided by the single centre experiences. Platelet rich plasma injected into the ovary had improved the ovarian function. Further research is required to identify the components that helped in the ovarian function and the patient characteristics (Sills et al., 2018).

MYTH: Anti-Mullerian Hormone (AMH) levels decrease in the presence of antiphospholipid antibodies (APA)

REALITY: In a study conducted about 50 women had elevated APA levels. After the adjustment of age, an association between the presence of APA and low AMH was seen. No other auto immune markers were associated with low AMH levels. However, further evidence is required to strengthen the results (Vega et al., 2016).

CONCLUSION

Due to several advances in infertility treatments, more than eighty per cent of infertile couples have children. Stem cells therapy is considered by the researchers because of their self-renewing and high differentiating potential property (Pourmoghadam et al., 2018). Stem cell therapy has paved path for people dealing with infertility. Further research and experiments would definitely strengthen this area.

RADHIKA THAPAR BAHL
Advocate and Advisor
Fertility Law Care (FLC)

LEGAL CONTROVERSIES IN ART

INTRODUCTION

In the past few years there has been tremendous scientific activity in the field of Assisted Reproduction Technology (ART) and correspondingly there is also huge demand as more and more people are seeking ART treatment. The growth in the ART methods is recognition of the fact that infertility is on a rise and act as a huge impediment in the overall well being of couples when they are unable to conceive through the conventional biological means. Relevance of Legality in ART: "Assisted Reproductive Technology", with its grammatical variations and cognate expressions, means all techniques that attempt to obtain a pregnancy by handling or manipulating the sperm or the oocyte outside the human body and transferring the gamete or the embryo into the uterus. The very fact that gametes are handled outside the body and through technological means pregnancy is aimed to be achieved, thus, in itself seeks for the intervention of law as the ardent defender of the rights of the parties involved and to be utilised as an instrument to protect the conflict of interests. In most of the scenarios there are gamete donation and /or renting of womb also involved, thus making the intervention of law inevitable. Lawsuits/ Legality not only helps in settling the score/ concerns between the opposing parties; they often help to incite social awareness of a prominent issue. Rule of Law: It is pertinent that no matter how unique, advanced, specialise, famous or socially well connected one is but in a civilised society and a country like India where law has been established and adapted as the basic norm of society; there it is the Rule of Law is superior and sacrosanct. Thus, Ig-

norance of Law is no excuse i.e., Ignorantia juris non excusat or ignorantialegisneminemexcusat is a legal principle holding that a person who is unaware of a law cannot escape liability for violating that law merely because one was unaware of its content. Thus, understanding the relevance of law and its importance in ART, lets now have a sneak peak into legal controversies in ART.

LEGAL CONTROVERSIES IN ART

At present in India, there is no enacted legislation on Assisted Re- productive Technology (ART) including surrogacy. Surrogacy Bill, 2019 has been cleared by the Lok Sabha but has not cleared the complete process to have the force of a Law. There are the "National Guidelines of Accreditation Supervision and Regulation of ART Clinics in India' issued by Indian Council of Medical Research, National Academy of Medical Sciences (India), New Delhi under the aegis of Ministry of Health and Family Welfare, Government of India in the year 2005 which has ethical binding on the Medical Practitioners and thus, the procedures are done as per the recommendations in the guidelines. The Guidelines provided a major break through to provide guidance and in establishing ART as a line of treatment but there are some key areas where guide- lines are silent and since, it is not a binding law on the general public, thus,makes it complex and difficult to set in accountability and check the misuse of technology which can disturb the established norms of the society.

1) Age Criterion to become a Parent: A further concern arises when clinics compete for favorable statistics by questionable patient selection criteria and treatment priorities. A 74-year-old woman has given birth to twin girls in the southern Indian state of Andhra Pradesh, reviving several controversies around geriatric pregnancies as well as the bringing up/ fate of children due to old age i.e., an age nearing or surpassing the life expectancy of human beings. This has become a huge concern and condemned by various doctor experts who believe and expect that in the pursuit to provide solutions to human desires, there should be reasonable restraint exercised. In the particular case, considering the old age of the lady, she should not be impregnated through the process of IVF. However, Mrs. Rao (the 74 year old), who was ecstatic after his daughters' birth, reportedly collapsed a day later after suffering a heart attack and had to also be admitted into the intensive care unit. The ICMR guidelines at present are silent about the maximum age of a Parent under IVF though the maximum age of surrogate is prescribed at 45 years. Interestingly, Shannon Clark, a professor of maternal and fetal medicine at the University of Texas Medical Branch at Galveston, said Yaramati's delivery is atypical but not sur- prising given the existing technology around assisted reproduction as reported in media.

2) Anonymous Donor: As per the ICMR Guidelines, the gamete donation has to be anonymous i.e., the recipient and the donor should not be knowing each other. The purpose seems to crystallise the parental rights in the favour recipient and to prevent the interest of the child so born but the Intended Parents in some cases want their known donor due to their own personal reasons but least realising that in future there could be lot of issues due to the access of Donor to the child. Also, taking an affidavit from the Patient or donor will not absolve the ART clinic/ doctor from the liability.

3) DNA Mismatch: IVF Mix-Ups have Broken the Definition of Parenthood, When a New York woman gave birth to twins after IVF, neither baby was related to her, or to each other.In this particular case, the clinic mixed up three couples embryos and the one couple lady who carried twins, delivered the babies of other two couples. Until the advent of IVF, the mother of a child was unquestionably the woman who gave birth to that child. The ability to create embryos in a petri dish and then transfer them into the womb introduced new nuances. occasional mistakes by IVF clinics have also created scenarios, like this one, of essentially involuntary surrogacy, which do not merely add nuance to traditional definitions of parenthood, but utterly confound them. When things go wrong with assisted reproduction we should look at what's best for everyone in the particular circumstances and in the interest of the child. On the basis of this, since the Biological parents were traced and more than willing to take the custody of the children so born, thus the court granted the custody in the favour of the couple. The courts in India are yet to arrive at a conclusive decision in such scenarios and usually the decisions are bent towards the best interest of the child. However, irrespective of the outcome of the decision, the Medical Practitioner can be prosecuted for negligence in such a scenario.

4) Guaranteed Package / Treatment: The Ethical code of conduct restricts a doctor from giving any guaranteed package / assurance of success of treatment.That "No cure/ no success is not a negligence", thus fastening the liability upon the treating doctor is unjustified. Hence, In several Consumer complaints, it has been upheld that no cure / no success is not a medical negligence and doctor cannot be penalised for the same unless it is proved that the doctor has given assurance or guarantee for the

success of the treatment.

5) Informed Consent: Informed consent, which blends law, medicine, and bioethics, is a multifaceted process to obtain patient permission and enhance patient understanding before health care interventions. Insufficient informed consent may even constitute battery or medical mal- practice.Assisted reproductive technology (ART) procedures have numerous ethical and medical considerations, including self-determination, affirmed through proper informed consent. Because procreative therapy is more elective than emergent, and multiple treatment paths may be reasonable, autonomy through informed consent is all the more important with ART. Information provides transparency to the procedure and helps the patient to take the rightful decision.

A 74-year-old woman has given birth to twin girls in the southern Indian state of Andhra Pradesh, reviving several controversies around geriatric pregnancies as well as the bringing up/ fate of children due to old age i.e., an age nearing or surpassing the life expectancy of human beings. This has become a huge concern and condemned by various doctor experts who believe and expect that in the pursuit to provide solutions to human desires, there should be reasonable restraint exercised.

6) Designer Babies or Abnormalities in the children Born through ART: That there have been a general perception in the understanding of many that through ART once can have a designer baby i.e., beautiful looking children and without having any problem are born and on the contrary many think that since it is not a natural process, so there are lot of abnormalities. It should be noted that there is no evidence to support the contention that children conceived through artificial reproductive technologies have any more abnormalities than the baseline found in the general population.[1] George Huggins & Anne Wentz, Obstetrics and Gynecology, 265 JAMA 3139,3140 (1991) (no evidence of increased chromosomal or congenital abnormalities).

Similarly there is no such concept of having the babies as perfect ones. Thus, such misconcep- tions should be done away with else it leads to legal controversies and misconceptions.

7) ART Procedure without Spouse Consent or Knowledge: The Court gives a lot of importance and sanctity of the relationship of Marriage and the first and foremost purpose of Marriage is com- panionship and then later comes reproduction. In a subsisting marriage i.e., means where marriage has not been Legally dissolved any such act would lead to penal implications against the spouse from hiding the information and also against the Doctor/ clinic. A case was reported in Mumbai, Maharashtra where in person proceeded as Single father / parent despite being married. On April 2, the State Commission for the Protection of Child Rights found the father, guilty of submitting a false affidavit to opt for the procedure. An order has been passed to initiate criminal action against him. The hospital, which carried out the surrogacy, has not been spared either, with the commission directing the formation of a task force to ascertain whether or not it followed medical guidelines in the case.In its final judgment, the commission found the Father guilty and said, "To initiate criminal action against the respondent number 4 and 5 (Father and his mother) under provision of Indian Penal Code for hiding the facts and preparing and submitting false affidavit.

8) Proper and Timely execution of documents: In a particular case, the surrogate was resisting to handover the custody of the child so born stating that she gave birth of the child for herself. The police investigated the matter and basis the documentation, the Intended Parents were able to get the baby in their custody. Making the Medical Practice on the basis that upon successful competition of a case the legal documentation will be executed could turn out to be fatal.

9) Proper Counselling: The legal and Psychological counselling also has a critical role to play. This helps in Intended parent and the other parties likes surrogates or the donors to understand their obligations and associated risks more clearly and later on cannot take undue advantage of stating ignorance of what they are entering into.

CONCLUDING COMMENTS

The Society to reap the true benefits of Assisted Reproductive Technological advancement, the Medical/ Clinical practices shall be in conformity with the established laws and norms of the society. In many social and ethical respects, natural and artificial reproduction are similar because they both fulfill the desire of parenthood and they both have the potential to burden children and society with the prospect of sub-optimal families. The difference between the two types of reproduction is not primarily moral-it is political and involved medico legal aspects from the very beginning of the process. The medical procedures necessary to carry out reproductive technologies render such assistance more vulnerable to legal intervention as compared to reproduction conducted in the bedroom. When a couple arrives at a fertility clinic, their parenting abilities are often scrutinized by doctors, hospital administrators and then qualifying the legal norms or paperwork is quite a handful but it saves many controversies or legal issues which may arrive later and jeopardise the interests of the parties involved.

From Stethoscope to Microscope

The Journey of a Doyen

Dr B.N. Chakravarty in conversation with

Dr Neha Priyadarshini

MYTHS & CONTROVERSIES

INTERVIEW

DR. NEHA PRIYADARSHINI
MD (Obs & Gynae), Fellow in Reproductive Medicine
Consultant - Satvik IVF, Dhanbad,
Founder Secretary - Jharkhand ISAR
Recipient of CL Zhaveri Award
Young Achiever Award by BJOGS

DR. DHIRAJ CHOWDHARY
M.Ch, MS, DNB
Director - Satvik IVF, Dhanbad

BEGINNINGS

Though I was born in Bangladesh, I didn't stay there for a long time. My father was an employee of the South Eastern railways in India so we moved wherever he was posted. Earlier he was posted in Tata Nagar in Jamshedpur, but then he got transferred to Jabalpur, Narayanpur and many other places. I stayed with my father till I was 5 or 6 years of age. Due to his frequent job postings in various places my education started suffering but soon I got settled in Chakradharpur in Bihar where I started my primary education. Slowly our family grew and I was blessed with brothers and sisters but financial woes started as well. Though it hardly affected me as I was good in studies and it helped me secure education scholarships.

I always dreamt of studying in Kolkata but my father's meagre earnings from his railway job to support a huge family of ten made me stay in Bihar. Those days Bihar's education system was a bit different to that of Bengal. We had to appear for the matriculation exam during class XI instead of class X and that cost me one extra year. But that didn't deter me as I not only topped my matric exams in Bihar but in the entire Chota Nagpur district and won yet another scholarship for higher education.

Fortunately I was able to realise my dream of moving to Kolkata but at the cost of letting go of my scholarship from Bihar as I would be studying under a different university. One of my friends from Kolkata landed a job in the railways and got posted in Chakradharpur. He was the one who helped give wings to my dream by sending me to his family in Kolkata where I taught his brother while pursuing higher education. So my basic need of fooding and accommodation was sorted. But admission to a college and tuition fees were a cause of worry as I was now deprived of my scholarship. I wrote a letter to Mr. Shyama Prasad Mukherjee with a copy of my matriculation result seeking his help for my higher studies. He called me and got me admitted to his father's college in Kolkata named Ashutosh College with a full waiver on my tuition fees but on a condition that I secure the first place in studies. Thanks to him and his condition that I secured the top position during my first year itself.

But later due to India's freedom struggle followed by partition and huge financial constraint I fell under a dilemma whether to continue studies or work to aid my father post the ISC examinations. Fortunately my friend's family supported me and my ambition, pushing me towards my aim of getting medical education. I got the chance of getting admitted to Medical College where the monthly fees was just Rs. 16 and I was able to pay it by providing tuitions. Fortunately I stood first in Gynaecology and won some medals which turned out to be a much needed incentive to continue my studies and do my MD. My teachers in medical college then helped me a lot and sent me to England to pursue Masters. Post my studies I started working and got financially stable. Then I got married and had two wonderful daughters. But due to some unavoidable reasons my marriage didn't last. I moved on and got married again but due to some complications we weren't able to have any more children. Today, only one of my daughters is alive and I am blessed with two grandchildren.

IVF THEN & THE DR SUBASH MUKHERJEE CONTROVERSY

We were doing this embryology in baby incubator with improvised trigas which had 5% carbon dioxide, 5% oxygen and 90% nitrogen. We used to get expired air inside a football balloon. Even though it was a tedious task we still used to do it as we were young and full of energy.

ISAR Express theme is Myths and Controversies. You have taken name of Dr Subash Mukherjee. There are different controversies regarding his personality, the work he did. Why due recognition not given to him? What were the different controversies regarding his career?

It became a controversy because the facilities were not available that time to bring out the embryological part but suddenly somehow he was able to do it. He had said about Vaginal Tubectomy which was very popular. He had also said that ovum can be retrieved by Colpotomy. At that time vaginal ligation was very common in India but vaginal Colpotomy was not. I never knew about it though we worked together, he had kept it well hidden from me. But after the news was out I confronted him. I hardly believed whatever he had said but he showed me how it was possible and asked me to work with him on it. He was a true genius and the work that he did was quite ahead of time. He had spoken about cryopreservation and this process itself led many to disbelieve his arguments. At that time cryopreservation was impossible as people believed the process required lot of electricity. Many criticized him as in order to achieve cryopreservation you needed to go a temperature as low as 196 degrees but it was hardly possible due to rampant power outage in Calcutta at that time. Those days we used to have just 4-5 hours of power supply everyday so how was it possible for the embryo to survive for a month. But his answer was liquid nitrogen. Now liquid nitrogen were already being used to store and transport embryos retrieved from animals and flown to different countries wherever required. This preservation process was in usage for the past 50 years atleast. I remember him say to me once that once you cut the metabolism it wouldn't require electricity and hence bring down the temperature. One of the ways anesthesia was given that time is by lowering the temperature. This was known as Cold stage anesthesia. Once you bring down the temperate, the patient does not require much oxygen and this brings down the metabolism. He came up with this idea from seal fish found in north and south poles because the fish there remain under the ice for six months and they survive. They remain cryofrozen for six months but when sun comes out and the ice melts, they become alive. He gave me this example but I didn't know that he was trying this theory

DR NEHA PRIYADARSHINI & DR DHIRAJ CHOWDHARY interview DR B.N. CHAKRAVARTY

on human ovum and embryo.

In cryopreservation, the embryo was preserved for one month. Nobody believed it in 1978. It came out officially in 1984/86 when someone did it in Holland and the first IVF baby was born through a cryopreserved embryo.

He had the vision that this can be done. This is very significant. To do this HMG was used but it was not available in its crude form. Those that was used was from animal source, it was not possible from a human source. He had the idea and did it in 1978.He must be given the credit and I believe it since I am one his closest associate. Though he had not done it but he started thinking about this method in 1974.

When this news on IVF came out in 1978, he was not believed by anybody as things were not available then. Powercuts were rampant, he didn't have a good laboratory, an ordinary incubator and he used an ordinary microscope to identify and dissect the follicles of the ovum inside a test tube. Just by identifying the color and how it shines in light, he used to deduce that the egg had come out of the follicle by seeing it through an ordinary magnifying glass. At that time Tyrode's medium was used. Ultrasound was rarely available. From day 1 of menstrual cycle, estrogen increases and Cervical mucus become thinner as the day of ovulation nears.

It was a difficult time. We used LHP (kit) and cervical mucus to determine the timing of HCG because we didn't have ultrasound to determine the diameter of the follicle.

These were Dr Subash's ideas. He transformed these into practice for monitoring and stimulating a patient and for picking up an egg and for cryopreservation.

LIFE'S DREAMS

Right from the very beginning, my life's biggest dream was to promote research. Since the year 1965 I started doing genitoplasty and vaginoplasty on women who weren't able to bear children, who had never menstruated, but that didn't deter me. This was not a job that paid well but I still kept on with my research. I always tell my students to not run after money rather to be patient and religious towards your work and money will come to you automatically.

Towards the end of my career I had already constructed two buildings dedicated to this cause which not only benefitted patients but also students and researchers. But then the future of the center came into question. My daughter wasn't interested to take care of it and my son-in-law who is an orthopedic surgeon didn't have much time to dedicate either. My grandson, a lawyer by profession, is a misfit. So it became very difficult to find a family member who was willing to take care of the institute. It is not about just having an interest but the medical experience coupled with passion to lead the center. The decision to handover the center to ICMR brought immense happiness to my family since they could see that the future of the institute lied in the right hands. If I had kept it with me then after my death it would have just remained like a property to be laid claim to by relatives for financial gains. If I had handed over to a corporate company, then it would turned into a money minting business that only treated patients. But by handing it over to the ICMR, I am assured that the future of the center will be brighter where research work would always be promoted.

MOTIVATION & PASSION

The force that drives me still is my passion to work. Secondly I want to motivate my juniors- the young doctors. The ones present at my institute didn't know much when they started in their career but today are more knowledgeable.

I have always followed my passion towards my profession and studies. Every time I stood by the vision that new things and new solutions can come up right here in my country but in order to achieve that you have to work and do a lot of research. This passion of mine kept me on my path towards progress without any diversion which could have fueled controversies.

ETHICS IN IVF

When we started working on IVF, we worked because of science. Now, most of the clinics work, albeit partially, because of the commerce involved in the science. Many invest in this science just to gain high returns.

Swami Vivekananda once said that if you donate money, knowledge or anything you have, do not expect anything in return. If you expect then your career and your ambition will all be futile. Everyone today expects return when they invest money, time and labour into creating a facility. But I believe in Swami Vivekananda's words, hence I am where I am today.

PROFESSIONAL INTEGRITY & MY LOVE FOR EDUCATION

Those who have been with me know that I have never betrayed anyone. I have always tried to share my joy and knowledge with utmost devotion to education. I believe this is what was truly accepted by my juniors. For instance, there was a boy Partho, who recently passed away, who had been with me since his 4th year of college. His father didn't like it initially as there was hardly much pay involved. Even today the pay is not what it is worth. Earlier there was hardly any pay involved. I used to pay them from the Ultrasound fees. But the training they received and the knowledge has helped my students grow in their careers. It was passion that bound the team together.

ON A 74 YEAR OLD WOMAN GIVING BIRTH TO TWINS CONTROVERSY

When I was the chairperson of the ICMR committee, it was decided that surrogacy shouldn't be allowed for a woman more than 45 years of age. I don't know why this happened. I guess this was done just to get fame. I remember this incident that happened 10 years ago with a 64 year old lady in Raipur who got pregnant. It was highly criticized by ICMR. It is very surprising that the same things happened again with a 74 year old lady. I feel the law should be strict and this shouldn't be allowed. It is a pity that there was no law governing IVF in 2002 when I was the chairperson of the ICMR committee until 2010. Though our committee tried to elucidate the need and formulate laws but the government didn't pass any laws or hard and fast rules governing surrogacy. These past 16 years, from the government to the ICMR, everybody strived to pass the law but somehow due to few people either in the government or the parliament the law couldn't pass due to their vested interest.

SCIENCE, BELIEFS, MYTHS & MIRACLES

More than myths, people feel that such scientific solutions are against their customs and cultural beliefs not to mention the affordability factor when it comes to faith healing. It is difficult for them to believe that the sperm from their own husband can fertilise their ovum within a controlled environment in a laboratory unless the woman herself is incapable of producing eggs or the sperm is incapable to fertilise the egg in which case a donor egg or sperm is used. Earlier people had this notion that only donor sperms are used in IVF. We had to convince them a lot. I remember my first successful IVF baby who belonged to Muslim parents. In their community surrogacy was still talked about a little but IVF was a big no. Though the father of the baby was a police constable but he still feared his society's backlash and asked me not to reveal their names when I broke the story of the IVF child.

Affordability is also in question when it comes to IVF. In fact I paid money from my own institute to ensure this IVF procedure is successful. But still acceptability among their culture and social customs is a very big factor when it comes to IVF. Today it is publicly accepted but affordability is still an issue.

HEALTH SECRETS

I am not into meditation or yoga neither I am a big foodie. I used to be a foodie during my younger days but as I turned 75, I started gaining weight and suffered from some heart ailments. I had to get a pacemaker but since then I started to go on morning walks and maintained a healthy diet.

TIME TO RELAX

I love to watch cricket. Though it is loved by the entire nation but my love for the sport began since my childhood days. I used to play cricket when I was in school. Though I was not a good player but I liked the sport. I recall when I was a resident doctor at Eden Medical College I had gone to see a cricket match with my friends. But when I returned to the hospital a patient undergoing D&C had died. It was an anesthetic death, no one saw her at the time and it caused me immense worry as I had not assigned her to someone else before leaving.

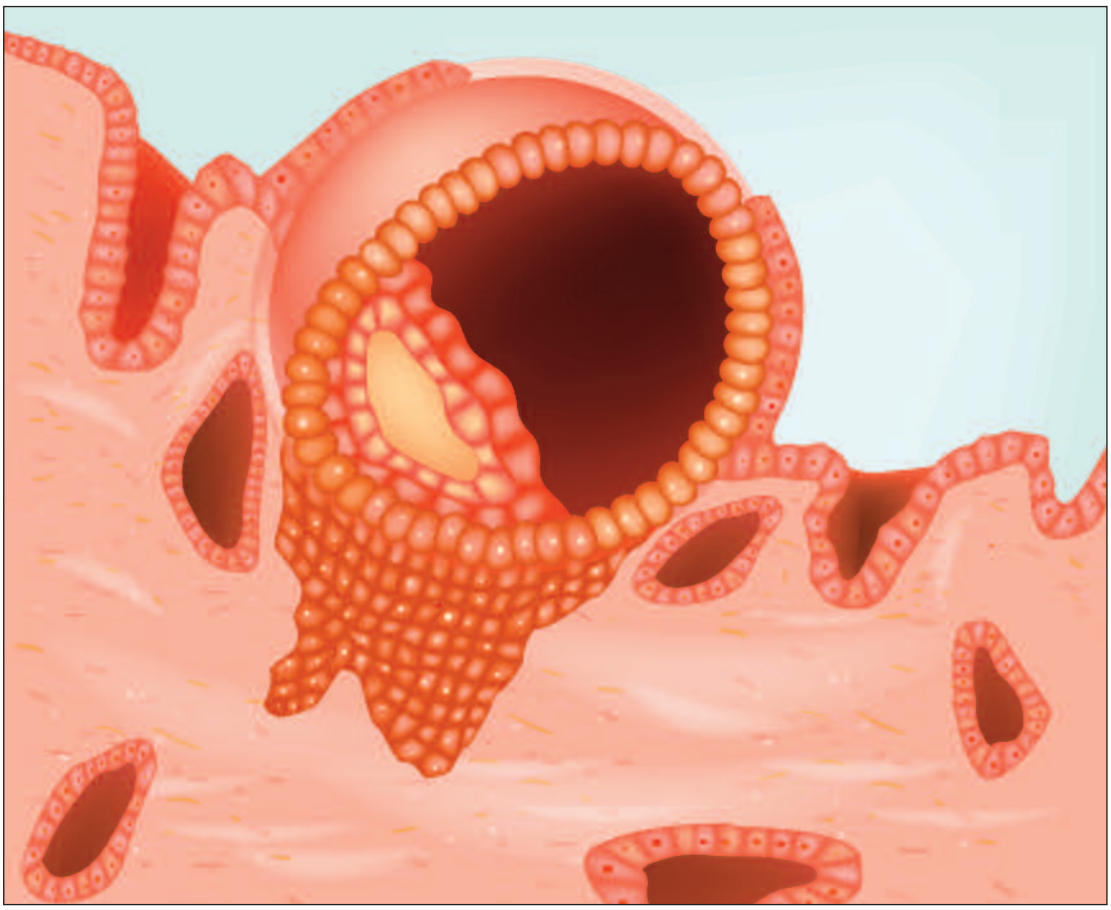
MESSAGE TO THE YOUNGER GENERATION WHO WANT TO PURSUE REPRODUCTIVE MEDICINE

Apart from dedication and devotion, I would say transparency. Don't say you are always doing correct things, audit yourself to see whether you are right or wrong. For instance when I went to see the cricket match and the patient under my care passed away, it was the worst mistake that I did. I should have assigned her to some other doctor before leaving. So I will always say that transparency and self-audit is very important to measure whatever work you have done before moving out for the day. This gives you a chance to rectify things before it is too late.

Revisiting the Science and Evidence on Sustaining Pregnancy

THE ROLE OF PROGESTERONE

DR MIRUDHUBASHINI GOVINDARAJAN
FRCS (Canada), FICOG
Director, Womens Center by Motherhood, Coimbatore
Specialist in Fertility Management at Womens Center, Coimbatore since 1994 with centers in Chennai and Trichy.



IMPLANTATION - THE BASICS

Successful implantation is the key for achieving a normal pregnancy. Implantationconsists of four essential steps, apposition, adhesion, penetration and infiltration. In order to facilitate this dynamic process,the endometrium undergoes phenotypic and genotypic changes termed"Endometrial Receptivity". The short period of time of approximately 48 hours in the luteal phase when the endometrial receptivity is optimal and maximal is called the "window of implantation".

ROLE OF PROGESTERONE IN ENDOMETRIAL RESTRUCTURING FOR IMPLANTATION

Progesterone is essential for the successful implantation and maintenance of pregnancy. It is the "hormone of pregnancy" and is responsible for the morphological(pinopods), vascular (angiogenesis), molecular(cytokines) and genetic changes in the endometrium. Progesterone also modulates the maternal immune system. It acts on maternal lymphocytes to synthesize a 34 kDa protein called PIBF – Progesterone Induced Blocking Factor –(Szekkerts – Bartho et al 1997).There is a shift from adverse Th1 cellular immunity, (TNF and interferon) to beneficial Th2 humoral immunity (IL4 & IL10). It also has an effect on NK cell activity.

ASSESSING THE PROGESTERONE EFFECT AND ENDOMETRIAL MODULATION ADEQUACY

Endometrium is a mixture of glandular epithelial cells embedded in a mesenchymal stroma. Both of

these components - epithelial gland and cellular stroma- change on a daily basis during a menstrual cycle. This allows for the daily "dating" of the endometrium due to progesterone effect. However, histologic dating alone is not an adequate test to determine all of the etiological factors for implantation failure.
The Clinicians ability to assess the endometrial changes using morphological criteria alone has been proved to be inadequate by COUTEFARIS et al. Current research is focusing on molecular markers for endometrial assessment.

CURRENT MARKERS FOR IMPROVED ENDOMETRIAL ASSESSMENT - CYCLIN E AND P27

Cyclin E and P27 are cell cycle regulators. They can reveal the underlying biochemical processes during endometrial progression and may represent the means by which estrogen and progesterone regulate this dynamic tissue. Cyclin E and P27 expression dramatically change in intensity and localization throughout the menstrual cycle. In the normal endometrium Cyclin E progressed from the basal subcellular location to lateral cytoplasm in the mid proliferative phase and on to the nucleus on day 18-19. It is found in the nucleus only for two days marking the receptive window. Itwas absent in biopsies after day d20.P27 was found only in the nucleus appearing on Day 17-19.

Since the publication of "Promise trial", several other RCT's have put forth the argument that the lack of benefit claimed in the trial was primarily due to the late start of progesterone. The claim was that vaginal progesterone if started in the early luteal phase will have better outcomes.

Cyclin E persisting after day 20 was more frequently found in infertility patients. Cyclin E and P 27 are found to be clinically useful markers of the endometrial development. DUBOWY et al have reported that abnormal and acyclic expression of Cyclin E in endometrial glands, (defined as greater than 20% after day 20 of the menstrual cycle) correlates with infertility and is a useful marker.

CLINICAL PRESENTATION OF PROGESTERONE INADEQUACY

Inadequate or inappropriate progesterone effect on endometrium can lead to defective implantation or early pregnancy losses. Recurrent Implantation Failures (RIF) or Recurrent Pregnancy Losses (RPL) may also result from these defects. Progesterone inadequacy can become a diagnosis of exclusion when all other problems such as anatomical, genetic, infectious and gamete related problems have been ruled out.

PROGESTERONE IN MANAGING RIF AND RPL

Changing perspectives

Cochrane review and meta-analysis (2013-issue 10: Haas DM, Ramsey TS) including 14 RCTS (2158 women) suggested that Progesterone supplementation could improve live birth rates in RIF and RPL (10). However in this review the included RCTs had heterogenous cohorts, various routes, dosing and timing of Progesterone administration. In some cases progesterone was started after bleeding occurred. Hence in conclusion a need for future studies was suggested to confirm the findings.
Kumar et al-Fertility Sterility 2014:102 RCT - oral progesterone treatment in early pregnancy to prevent RPL and its role in modulation of Cytokine production. Reported that the risk of miscarriage was 2.4 times higher in the placebo group vs. progesterone group. There was significant improvement at the age of gestation at delivery
"Promise trial" – 2015 by Coomarasamy et al in NEMJ
This large multicenter trial on efficacy of vaginal progesterone in RPL did not support previous Cochrane review.The study concluded that progesterone therapy did not result in a higher live birth rates.

PROGESTERONE IN RIF AND RPL- CURRENT VIEW POINT

Since the publication of "Promise trial", several other RCT's have put forth the argument that the lack of benefit claimed in the trial was primarily due to the late start of progesterone. The claim was that vaginal progesterone if started in the early luteal phase will have better outcomes. Some recent studies have modified their RCTs to test this hypothesis. In these studies besides clinical outcome, newer molecular markers have also been used to further assess the beneficial effect of progesterone in the luteal phase.

LUTEAL START PROGESTERONE AND PREGNANCY OUTCOME - *A review of recent studies:*

Several studies have used newer molecular markers as well as pregnancy outcomes to study the effect of luteal start vaginal progesterone. Better outcomes have been reported with this change in protocol.

Study I - Luteal start of micronized vaginal progesterone and pregnancy success in RPL

Mary Stephenson et al. F/S. March 2017
116 women with RPL – RCT – **Luteal start vaginal progesterone vs placebo.**
Pregnancy outcomes as well as N Cylin E marker was studied. N cyclin E was assessed to monitor progesterone effect on endometrium. Outcome showed **improved pregnancy rates (68% Vs 51%) as well as normalization of markers. It concluded by recommending that since vaginal proges-**

terone is relatively inexpensive and safe, empiric interim use of luteal start micronized vaginal progesterone in RPL.

Study II -Randomized double blind controlled trial for vaginal progesterone in RPL

Alaa.M.Ismail et al. Journal of Maternal, Foetal, neonatal medicine 2017

• 700 women on luteal vaginalprogesterone support - Participants were randomly assigned to receive either 400 mg vaginal progesterone pessaries or placebo twice daily, started in the luteal phase and continued after a positive pregnancy test till 28 weeks of gestation.

• Clinical outcomes and inflammation markers were assessed.

• Cytokine levels through all three trimesters were measured. Significantprogressive increase in the beneficial cytokine IL-10, and decrease in IL-2was found. A striking beneficial immune modulation effect by progesterone was documented.

• Clinical results showed decrease in miscarriage rates (12.4% vs 23.3%) as well as Increase in live birth rate (87.6% vs 76.7%)

ROLE OF ENDOMETRIAL TESTING IN CLINICAL PRACTICE:

There are three commercially available tests Worldwide for endometrial assessment at the moment.

• ***ERA – Endometrial Receptivity Analysis (Iviomics - Spain)*** is a molecular array based means of dating the endometrium. No information is obtained on other pathologies.

• ***EFT – Endometrial Function Test (Yale Univ.– USA)***

o There are Two components to this test -

o Histologic assessment as well as several molecular markers. It is feasible to assess the dating as well as the functional maturity of the endometrium. Cyclin E is one of the molecular markers. There is feasibility of diagnosing other inflammatory and infective pathology also.

• ***Receptiva DX –***

o Immuno histo chemical expression of βcell - BCL 6 is assessed.

o BCL – 6 is an Inflammatory marker specifically associated with endometriosis

o Specific test to assess the inflammatory changes in the endometrium secondary to pelvic endometriosis.

CONCLUSION:

RPL occurs in about 2% of couple trying to conceive. **In a vast majority of RPL and RIF, the cause remains unknown even after investigations. One of the causative factors may be inadequate progesterone activity during luteal phase.**

Recent trials studying the Progesterone effect on endometrium in RIF and RPL have reported improvedoutcomesafter administration of luteal vaginal progesterone. This has been confirmed by recent studies reporting clinical outcomes as well as current laboratory parameters for metabolic markers.

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1. Cochrane review and metaanalysis (2013-issue 10: Haas DM, Ramsey TS)
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Q&A YOUNG ACHIEVERS Coffee with Dr Gautam Khastgir

DR. S.M. RAHMAN
MBBS, MD - Obs & Gyn

What is the most effective development in the field of ART in the last decade?
There have been many developments in the field of ART. Some are:
1. Oocyte quality enhancement by Mitochondrial transfer by using spindle view technology.
2. IMSI where sperm morphology and organelles can be seen in 7,300 X.
3. Spindle view technology for doing ICSI.
4. Time Lapse Imaging or Embryoscopy for understanding better morpho-kinematic of developing embryos for selected embryo transfer.
5. Oocyte freezing.
6. PGS with current NGS technology after day 5 multi-cell trophectoderm biopsy, has replaced the old day-3 single blastomere biopsy and is thought to have a improved embryo implantation rate.
7. Microfluidics in sperm selection.
8. MACS for better sperm selection.

Which myths or misconceptions have been detrimental towards acceptance of the ART?
There are several myths like:
1. People think IVF always works.
2. These are only options for couples struggling with infertility.
3. Babies conceived through ART will have a higher chance of birth defects, low birth weight or developmental delays.
4. A lot of people think that they will have to be on bed rest throughout the pregnancy period.
5. Another misconception is about use of donor gametes.

What steps can be taken to make ART available for masses?
One of the major steps is a nationwide network of top fertility clinics offering discounted treatment packages and financing. It will allow every section and class of people to avail this treatment in a wide manner. Low Cost IVF with good success is the solution. Also, I feel through my entire career that extensive mass education about various fertility treatment options, about the dos and don'ts in their life style, and educating the mass about every misconception about infertility at ground level, are much needed. Because as per my understanding, it is lack of knowledge about infertility as a whole beside the high cost factor which are negatively working in the Indian context.

DR SUJOY DASGUPTA
MS, DNB, MRCOG
Gynaecologist & Infertility Specialist

What is the most effective development in the field of ART in the last decade?
Embryo cryopreservation made the segmentation of ART easier, helping transfer of the embryo in right time without compromising the success rate. It is particularly useful in fertility preservation and OHSS. The widespread use of antagonist protocol and selective use of agonist trigger made ART safer by significantly reducing the risk of OHSS.

Which myths or misconceptions have been detrimental towards acceptance of the ART?
Majority of the people have an idea that ART is something "totally artificial" and there would be increased chance of congenital anomalies. Many believe that success after IVF is rare and it will eat up all their savings. Some people think that IVF is a very painful procedure and after the transfer the patients need complete bed rest. Another popular myth is that ART is the last resort of fertility treatment and should be done only after exploring all the possible options and spending years after years.

What steps can be taken to make ART available for masses?
The need of the hour is public awareness programme involving the couples who went through IVF and their kids. This will help people understand that IVF-pregnancy is not different from natural conception, without increased risk of complications or congenital anomalies. We need transparency regarding the costs of the procedure and should try to minimize it by rational investigations and rational use of medicines. The Govt and the insurance companies should also come forward to minimize the financial burden. We should refrain from advising complete bed rest, because there is no evidence that it improves the outcome. Finally, there should be a evidence based national guideline on IVF so that all the practitioners can sing in the same tune.

DR INDRANIL SAHA
MD, MRCOG, Post CCT
Senior Consultant, Genome Fertility Center

What is the most effective development in the field of ART in the last decade?
The two most effective development that have taken place in the field of ART in the last decade are:
(i) Vitrification
(ii) Introduction of Commercial Media

Which myths or misconceptions have been detrimental towards acceptance of the ART?
There are certain misconceptions which have been detrimental towards the acceptance of the ART. The most common ones are:
(i) Couples get pregnant once they go through IVF
(ii) Choice of gender of baby can be pre-determined by IVF
(iii) Age of female partner is not a factor
(iv) Baby has an high risk of birth defect
(v) It can resolve all fertility issues

What steps can be taken to make ART available for masses?
The most primary yet important steps that can be taken are:
(i) Minimal stimulation that employ relatively reasonably priced oral fertility drug followed by low doses of injectable gonadotropin
(ii) Controlling prices of gonadotropins so that they are within the budgetary reach of the common masses
(iii) Increasing women's awareness regarding ART as length of awareness and attitude towards ART influences outcome of fertility treatments.

DR. GAUTAM KHASTGIR

MD, FRCS, FRCOG, FICOG
Medical Director - BIRTH, Kolkata

SPONDITA BANERJEE

M.Sc in Clinical Embryology & PGD
M.Sc in Medical Biotechnology

What is the most effective development in the field of ART in the last decade?
The most effective development among the widespread technologies used in the field of ART, over the last decade is Time Lapse Technology (TLT).

Which myths or misconceptions have been detrimental towards acceptance of the ART?
Some of the myths are:
- Too Costly & low chance of success
- It is only for young partners
- Fear of confidentiality & social stigma.
- IVF takes away eggs that you would have and diminishes chances of naturally conceiving for whole life.
- Ovarian stimulation causes ovarian cancer and other health hazards.
- There is zero control over ovarian hyper stimulation in IVF and it can cause death
- IVF babies are born with abnormalities
- IVF pregnancies lead to Caesarean births.
- Infertility is a shortcoming of the female partner.

What steps can be taken to make ART available for masses?
- Removing social stigma
- Introduction of ART as special compulsory curriculum in syllabus of various Under-Graduate courses.
- Writing fertility blogs and sharing them on social platforms.
- Performing several campaigns emphasising the utility of ART throughout the year among non-medical personnels.
- Cover ART under medical insurance
- Setting up of at least basic ART facilities in all government hospitals.

What is the most effective development in the field of ART in the last decade?
Some of the advancements are:
Soft stimulation, OHSS free clinic, Improving oocyte quality (by transferring Co-enzyme Q10 supplementation or Mitochondrial transfer), Time-lapse imaging, PRP use in RIF in IVF cycle and in reduced ovarian reserve, elective Single Embryo Transfer (eSET).
Besides these achievements, some novel methods are being introduced to improve oocyte quality in older women with new stimulation protocols, that may improve the no of mature oocytes retrieved during an in-vitro fertilization cycle. However, some biotechnological application like pre-implantation genetic testing (PGD/PGS) has begun a new era of faith and hope on ART.

Which myths or misconceptions have been detrimental towards acceptance of the ART?
There are many myths and misconceptions surrounding IVF and other ART in people. Actually, the reality is that many of them are only due to lack of enough knowledge regarding these procedures. Clearing these misconceptions can help to remove the social stigma associated with these techniques as well. Here are some such myths /misconceptions.
1. Infertility is a female problem
2. If a man can ejaculate, his fertility is fine
3. It is only for the rich
4. IVF has a 100% success rate
5. Babies are born with birth defects and malformations
6. Poor acceptance to donor gamete / third party involvements
7. Donating eggs will deplete them
8. ART is only for younger couples
9. IVF can resolve all infertility issues
10. IVF is not safe
11. IVF requires a person to be admitted in the hospital
12. IVF leads to multiple pregnancies
13. IVF pregnancies result in cesarean births

3. What steps can be taken to make ART available for masses?
The following steps could be taken/considered to make ART available for the masses:
Reducing cost of IVF cycle, Educating people about infertility through camps/NGO, Media promotion, Making service available in government hospital, Sponsorship.

DR. SNEHASISH SARKAR

MS, Ph.D. from IIT-KGP
Embryologist
IIH-Dum Dum,
Kolkata

What is most effective development in the field of ART in the last decade?
The field of ART is rapidly progressing with many new advances in the last decade. Some are:
A. Improving oocyte quality with new stimulation protocols.
B. TIME-LAPSE IMAGING TECNIQUE(TLI)
C. PGS
D. New approaches to assess the receptivity of the endometrium (ERA method).

Which myths or misconceptions have been detrimental towards acceptances of the ART?
There are many myths and misconceptions surrounding IVF and other assisted techniques. Some such myths are:
A. It has a 100% success rate.
B. IVF babies are born with birth defects and malformations.
C. IVF is not safe.
D. IVF leads to multiple pregnancies.
E. Pregnancies result in cesarean births.
F. Impotency and infertility are the same.

What steps can be taken to make ART available for masses?
The most prohibitory aspect about ART'S mass availability is the price of the procedure and the training of professionals.
A. The government needs to wake up to substantial prevalence of infertility of our society and it's growing number.
B. Offer super speciality courses in government medical college, so that more specialist doctors could be available.
C. The cost of hormone should be regularized and made uniform.
D. Similarly, the cost and availability of media used in IVF is very restrictive.
E. Another bottleneck in ART is availability of well trained embryologist. Very few government institutions offer embryology courses.This should be corrected.
F. Medical insurance cover for ART.
G. Most importantly, educate the masses about it with TV shows, advertisements, college program..Try to remove the stigma attached to it and present it like any other medical condition, easy to treat.

MS SABINA YEASMIN

Chief Embryologist
Indira IVF Group

Towards Better Practices, Better Outcomes.

YUVA ISAR 2019

"The world is but a Canvas to our Imagination"

YUVA ISAR 2019 was indeed one of the best conferences of the year and entirely focused to the Youth, For the Youth and With the Youth.
It was a conference focused to teaching and bringing in new innovations in the academic theme of the conference **"TOWARDS BETTER PRACTICES BETTER OUTCOMES"**

Agra, the beautiful city of love welcomed each delegate and faculty with lovely hospitality. The program was extensive and exhaustic including Hot Debates, Evidence Based Practices, Latest Guidelines, Best of the Faculty and Amazing Entertainment. It was a Marvelous Academic Feast.

Our first "Out of Box" event was the Yuva Orators. Applications of more than 30 received, out of which 6 Orators presented a "Med-Talk"at the inauguration of the conference.

Highlight was our foreign faculty.

A superb public forum was also planned on ***#MainBaanjhNahinHoon***.

College days were relived with the interviews of ISAR Dr Manish Banker Award Applicants.

From 16 August to 18th August, there was a high energy level amongst all.

Ian Donald ISAR Course was a Big Hit.

An amazing session and unique thought by Dr Jaideep Malhotra was the Training of Paramedics ISAR Fertility Support Course.This is the need of the hour for all fertility clinics to really give better outcomes.The course was attended by 16 nurses and technicians who were made to understand the basics of RTE and a great feedback was given by all another highlight was each hall had one your research paper presentation by Yuva you have done good research in air the best of the conference was also actively participated.

Fertility Nurses and Support Staff Training

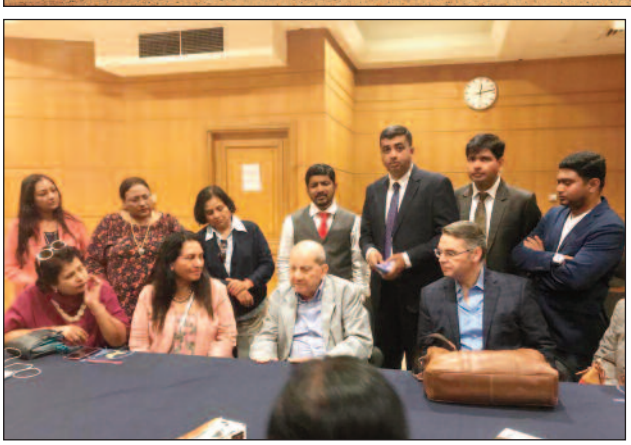
16 August 2019 was a historic day for YUVA ISAR 2019 in that it was for the first time in India that a workshop for the Fertility Nurses and Support Staff Training was flagged off in Agra under the leadership of Prof (Dr) Jaideep Malhotra. This workshop was conducted by AGK Apollo MedSkills Kolkata. Nurses from various hospitals in and around Delhi and UP, along with a couple from other states and abroad attended the workshop. It was a runaway success with great enthusiasm shown amongst the participants.

The workshop was inaugurated by Professor Saroj Singh, Past Principal and Head of the Department of Obstetrics & Gynaecology, S N Medical College in the presence of Professors Jaideep and Narendra Malhotra along with the Nursing Superintendant. The programme started off with a talk on Female and Male Reproduction – Physiology of Conception and was followed by a talk on Epidemiology of Infertility – Effects of Age and Lifestyle. The next was a session on Laboratory Investigations for Infertile couples. The pre-lunch session also covered the topics of Psychological Wellbeing and Support of Infertile Couples, as well as Ultrasonography, Hysteroscopy and Laparoscopy.

The post-lunch session opened to a packed house with a video demonstration on the techniques of Gonadotropin Dose Calculation and Subcutaneous Injection using a pen device. This was followed by an emotive session on Quality of Care, Dignity of Couples, Ethics and Safety of Treatment. Finally, the Clinical and Laboratory Aspects of Assisted Conception were covered for better understanding of the participants so that they can counsel their patients effectively on a day to day basis.

Professors Jaideep and Narendra Malhotra moderated the question answer sessions and explained in local languages to all the nurses, making the session as a very interactive one. The workshop ended with an interactive session between the faculty and the participants. The faculty included Dr Aparna Khastgir, Dr Gautam Khastgir and Mr Niladitya Sanyal. The question and answer session was followed by the filling up of feedback forms and distribution of Workshop Participation Certificates. The overall feedback has been extremely encouraging and has led to several requests from other such organisations and individual clinics to conduct similar workshops in their respective states.

The Artosscopia - Hysteroscopia Conference



The Artosscopia -Hysteroscopia conference on the Nile had a daily afternoon round table meet while sailing from Aswan to Luxor on The Sonesta Moon Goddess

But the most Enriching experience was the Egypt University course arranged by Prof. Osama Shawki on 5th October, 2019 at Cairo University School of Medicine, Kasr Al Ainy.

The Scientific Programme began at 10.30 am with 35 enthusiast Indian doctors, led by IAEC President Dr Varsha Baste and ISAR President Dr Jaideep Malhotra.

Eminent delegates included FOGSI Past- Presidents Dr Sadhana Desai and Dr Narendra Malhotra and Former FOGSI Vice Presidents Dr M.C Patel & Dr Maninder Ahuja and well known IVF teachers Dr Purnima Nadkarni and Dr Kishore Nadkarni.

The Egypt University Course started by introduction by Prof Osama Shawki.

Prof. Mohamed Aboul Ghar, senior most Gynaecologist from Egypt addressed us on 'The Story of IVF from Microcosm to Macrocosm ART Yesterday, Today & Tomorrow.' He described his valuable experiences and the initial difficulties he had in setting up the IVF programme in the country and reiterated the importance of 3-D Ultrasonography in diagnosing Muellerian Anomalies.

Prof. Ahmed Al-Minawi, GynaecOnco-Surgeon, explained to us the entire history of the founder Dr Mahfouz and about his Atlas, in the museum.

The delegates were spell bound by the technology of

presentation wherein the wall was used as a touch screen and high resolution videos of Dr Mahfouz's surgeries including VVF repair were demonstrated.

The museum included a copy of the famous Atlas on Gynaec surgeries by Prof. Naguib Pacha Mahfouz .

Also there were innumerable specimens of Anomalous foetus', Rupture uterus specimens, and Conjoined Twins.

Later, we were honoured to visit the office of the Dean, Prof. Hala Salah. Prof Osama Shawki introduced us to Dean madam who welcomed us with utmost hospitality .

Dr Jaideep Malhotra, in her talk opens out a concept of Academic exchange of students between India and Egypt for mutual benefit and sharing of knowledge and it was welcomed by the Dean.

Subsequently , there was a working lunch , where we enjoyed a lovely local Egyptian biryani calked Kosheri.

The first lecture was chaired by Dr Narendra Malhotra and Dr Purnima Nadkarni. Prof. Hassan Gaafar, spoke on Ultrasonography in Gynaecology and Infertility and elaborately covered from the basics to advance Contrast Sonography and importance of measurement of utero-cervical angle for Embryo transfer.

The second lecture was chaired by Dr Jaideep Malhotra and Dr M.C. Patel.

Dr Hasan Salam, took us through the entire journey of IVF, from the basics to the advances in Genetic technologies.

There were talks by -

Dr. Varsha Baste: Stem cell & it's future.

Dr Jaideep Malhotra: Genetics and human reproduction

Panel on ART : Moderators:

Dr. Sadhana Desai, Dr. Poornima Nadkarni

ART panelists:

Dr. M.C. Patel, Dr. Maninder Ahuja, Dr. Rupal Shah, Dr. Pratibha Singh, Dr. Manjushree Boob, Dr. Jyotsna Daule, Dr. Prerana Shinde

Panel on Hysteroscopy:

Moderators: Dr. Nitin Shah & Anurag Bhate

Panelists:

Dr. M.C. Patel, Dr. Ganpat Sawant, Dr. Samir R Pradhan, Dr. Pankaj Mate, Dr. Bansi Shinde, Dr Santosh Jaybhaye, Dr. Gautam Khastgir, Dr. Rajeev Shinde.

The Academic session was concluded by a vote of thanks by Dr Narendra Malhotra and distribution of certificates to the delegates and felicitation of Egyptian speakers.

ISAR president Dr. Jaideep Malhotra announced two fellowships through ISAR for endoscopy from India & The Dean Cairo announced two fellowships from Egypt too for endoscopy trainning exchange programmes.

ISAR EMBRYOLOGY CONSENSUS

DR KESHAV MALHOTRA
MBBS, MCE

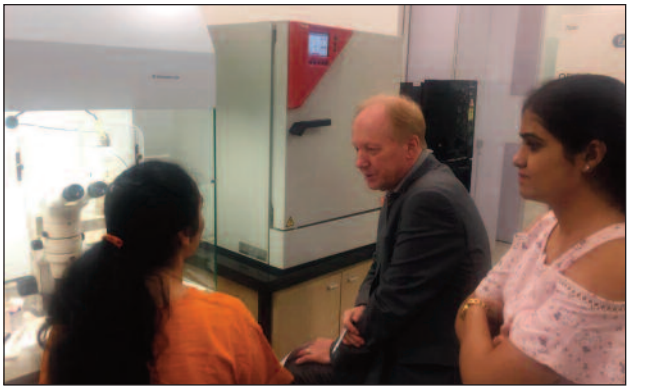
Standardisation is the only way forward and this year ISAR has primarily focussed on standardising infertility practices throughout the country. The embryology consensus which was the first major undertaking of Dr. Jaideep Malhotra, had its final stakeholder meet in Mumbai on the 27th of September. The meeting was attended by over 100 stakeholders including Clinic directors, Lab Directors, International Advisors, Pharma, and public representatives. In the last 6 months the moderators and their respective groups worked hard on creating documents which would serve as a standard reference for anyone who wants to practice embryology in the country. They worked of three critical topics- Safe and Ethical practices, Add on treatments and Pre-implantation Genetic Testing. The meet was preceded by a one on one session with the International advisors Dr. Steven Fleming from Australia, Dr. Inge Errebo Agerholm and Dr. David Hansen from Denmark. This one on one session helped the moderators fine tune the drafts which were produced and helped them have an international perspective on the same. The moderators then proceeded to produce the drafts to the stakeholders, taking in the stakeholder comments and deliberating and debating on whats best for the country with the best in the country. The meet was chaired by experts in the field –Dr. Jaideep Malhotra, Dr. Hrishikesh Pai, Dr. Rishma Pai, Dr. Duru Shah, Dr. Prakash Trivedi, Dr. Ameet Patki, Dr. Madhuri Patil, Dr. S Krishnakumar, Dr. Kedar Ganla, Dr. Kanthi Bansal, Dr. Raju Shaetya, Dr. Deepak Modi and Dr. Vijay Mangoli. Through these deliberations we've been able to fine tune our documents and they are now ready to be published. This is a landmark activity for the country as well as the subcontinent as nothing like this exists here and ISAR takes pride in acknowledging the efforts of the President Dr. Jaideep Malhotra, Embryology Chair, Mr. Sudesh Kamat and all moderators and members of the consensus Groups.

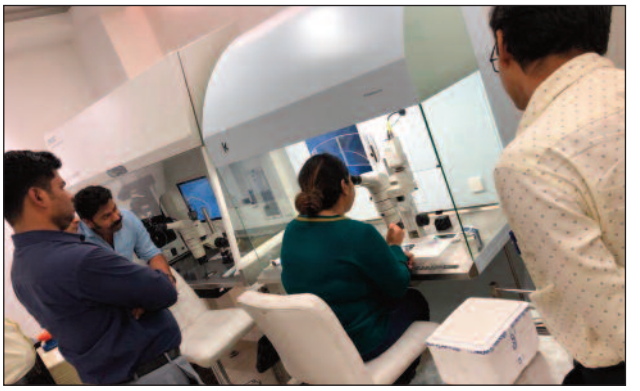
CONTRIBUTORS IN EMBRYOLOGY CONSENSUS:

1. Jaideep Malhotra
2. Sudesh Kamat
3. S. Krishnakumar
4. Kedar Ganla
5. Keshav Malhotra
6. Priya Kannan
7. Pankaj Talwar
8. Gaurav Majumdar
9. Ritu Hari
10. Akanksha Mishra
11. Charulata Chatterjee
12. Seema S Nair
13. Pranay Ghosh
14. Rajvi Mehta
15. Harsha K Bhadarka
16. Sapna M Srinivas
17. Lalith Kumar
18. Rushika Mistry
19. Deepak Goenka
20. Gaurav Kant
21. Prabhakar Singh
22. Nishad Chimote
23. Sachin Bawle
24. Saroj Agarwal
25. Pooja Awasthi
26. Ram Prakash
27. Yogesh Kumar
28. Charudutt Joshi
29. Vijayakumar Chelur
30. Sayali Kale Kandari
31. Dayanidhi Sharma
32. Nishad Chimote
33. Manjeet S Mehta
34. Sarabpreet Singh
35. Feseena Sethi
36. Dharmesh K Kapadia
37. Rohit Gutgutia
38. Vijay S Mangoli
39. Sanjay Shukla
40. Raju R Sahetya
41. Ratna Bhai Agrawal
42. Krishna Chaitanya
43. Priya Selvaraj
44. Shailaja Saxena
45. Ratna Chaterjee
46. Ved Prakash

ISAR –ORIGIO

ADVANCE EMBRYOLOGY COURSE & SKILL CERTIFICATION





ADVANCE EMBRYOLOGY COURSE

Under the innovative leadership of President ISAR, Dr. Jaideep Malhotra, ISAR this year conducted The ISAR Advanced Embryology Course & Skill Certification to upgrade the knowledge of our embryologists & help them have a better understanding of the recent technological advances in the field. This course was conducted in collaboration with Cooper Surgical from 23rd to 28th September 2019 in Mumbai, and was divided in three parts.

Day 1, Embryological Advances, which covered advances in Sperm Selection, Laser Assisted Hatching and advances in Culture Media.

Day 2, Oocyte Freezing, which is gaining a lot of awareness among patients and therefore the whole day was dedicated to understand the nitty gritty of oocyte cryopreservation with ample hands on experience.

Day 3 & 4, Embryo Biopsy, This module covered the basics of embryo biopsy including demonstrations and hands on experience in doing embryo biopsy and understanding when to do PGT, How to do it & Why to do it?

The course was well attended and had rave reviews.

We thank the faculty Mr. Sudesh Kamat, Dr. Rajvi Mehta, Dr. Keshav Malhotra, Ms. Atita Shinde, Dr. Sayali Kandari, Dr. Krishna Chaitanya & Dr. Steven Fleming.

SKILL CERTIFICATION

This was followed by the first ever Skill Certification Programme for India. The Skill certification was done for ICSI & Vitrification. 4 Candidates appeared for the exam which included a 30 MCQs objective paper followed by a practical exam conducted by Dr. Steven Fleming (Australia), Dr. Inge Errebo Agerholm (Denmark) & Mr. Sudesh Kamat & Dr. Keshav Malhotra.

This certification is the first certification of practical skills of Embryologist, which by far is one of the most important validations for any embryologist working in the IVF Laboratory.

Congratulations to the candidates Ms. Sapna Gandhi, Mr. Chand Mohamad, Ms. Meha R. Desai & Ms. Dhruti K. Thakkar for successfully clearing the exam.

Dr A Suresh Kumar
Chairperson

Dr Tripti Nagaria
Secretary

Dr. Ratna Agrawal
Acting General Secretary cum Treasurer

CHHATTISGARH

Chhattisgarh chapter of ISAR, organized a TRAVELLING SEMINAR ON "THE OVARIES: UNDERSTANDING OVULATION, LUTEAL PHASE & IMPACT OF ENVIRONMENT".

It was a half day Seminar from 10:00 AM to 02:00 PM with breakfast, lunch and Hi-Tea in mid-session.

The program started with the formal inauguration by lighting the lamp of wisdom and flag hoisting. The welcome address video of Dr. Jaideep Malhotra was shown followed by Making Parents video & a welcome note by the Chairperson of CG Chapter of ISAR, Dr. A. Suresh Kumar. National Guest speakers of the day were Dr. Archana Baser from Indore & Dr. Siddhartha Chatterjee from Kolkata. Eight local speakers were also there. Dr Sweta Agrawal & Dr Nupur Bharti were the Master of ceremonies. Mr Manoj Taneja head of Spectra Team

also helped us to make this program successful. About 120 delegates, dignitaries & Business delegates attended the Seminar.

Dr Shanti Roy
Chairperson

Dr Pragya Mishra Choudhary
Secretary

BIHAR

13th October 2019, Sunday

A CME was jointly organized by Bihar Chapter of ISAR & Patna Obstetric & Gynecological Society at Hotel Panache, Gandhi Maidan, Patna from 11.30 AM onwards.

Subject: Transdermal Usage of Estradiol in Infertility & Hormone Therapy

Speaker: Dr Gautam Khastagir, Kolkata

Chairpersons: Dr Neelam, Dr Usha Didwania

Subject: Role of Gonadotrophins in IUI Stimulation

Speaker: Dr Himanshu Roy

Chairpersons: Dr Barunkala Sinha, Dr Vinita Singh

Subject: Acute Venous Thromboembolism in Pregnancy

Speaker: Dr Pragya Mishra Choudhary (Secretary, ISAR Bihar Chapter & POGS)

Chairpersons: Dr Usha Sharma, Dr Amita Sinha

ANDHRA PRADESH

Dr Padmaja V
Chairperson

Dr Chandana V
Secretary

ISARAP, in association with VOGS and Sun Spectra Division conducted a regional summit on 15/sept/2019 at Hotel Novotel in Vijayawada.
The members of AP chapter of ISAR who attendend the ESHRE Annual Conference at Vienna shared the knowledge gained from various pre-congress workshops.
Dr. V Padmaja, chairperson talked on early pregnancy loss, Dr sajjaPadma: Pre-ART Optimisation
Dr Kavithach: Unexplained Infertility
Dr Chandana V: Consensues on Recurrent Pregnancy Loss
Dr. Prashanthi : Surgery for Fertility Preservation

Session 1: was Chaired by Dr. RS Rama Devi & Dr Prabhadevi
Going beyond contraception with the fourth generation pill: National Faculty: Dr. Sri Lakshmi G
Confidence of evidence: Vaginal Prog in LPD, RPL, PTL: Dr. Aruna Kumari, Rajamundry

Session 2: Chaired by Dr. Hima Bindu & Dr Geeta Devi
Redefining Iron Supplementation: The New Generation Oral Iron: National Faculty:Dr Jyothika V Desai
Predict, Prevent and Manage PIH: Dr Uma M
Quiz on PIH was held by the quiz team: Dr Himabindu, Dr Usha Prasad, Dr Ratna
followed by lunch

Session 3: Chaired by Dr Chandrasekher, Dr Lakshmi Narayana
Reviving fertility importance of anti oxidants in male and female infertility: Dr Sujathavellanki
Panel Discussion: Induction of ovulation case scenarios was moderated by : Dr Chandana, Dr Kavithach
Panelists: Dr Rama Krishna Hanuman, Chirala, Dr Vani, Eluru, Dr. Karuna, Vijayawada , Dr. Anitha, Vijayawada.
Quiz answers, Certificate distribution and prize distribution to quiz winner was conducted followed by a vote of thanks.
2 credit hours by AP Medical Council
This meeting was attended by about 195 doctors from various regions of Andhra Pradesh.

Dr Gulpreet Kaur Bedi
Chairperson

Dr Pooja Mehta
Secretary

CHANDIGARH

AUGUST - On 9th August a talk was held at the Oby & Gynae department of Kamla Nehru Hospital on high risk pregnancy, its outcome and management. There was good interaction from the audience of about 50 gynaecologists of the institution. A state level infertility conference was arranged by IVY IVF Centre, Mohali Obs & Gynae Society and ISAR Chandigarh Chapter. Deliberations on IVF Lab Setting, Fibroids and fertilty issues, and medico-legal problems faced by the fraternity were the highlights of the event. Dr Rimmy Singla, the organizing secretary and about 150 doctors made this a great learning feast.

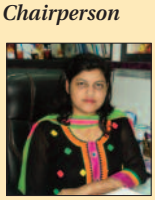
SEPTEMBER - A CME on PCO in adoloscence and infertility was held at Ludhiana, in collaboration with the Ludhiana Obs & Gynae Society on the 26th of September. With Dr Hrishikesh Pai and Dr Pooja Mehta as speakers it was well attended by the local doctors.

A meditation camp with stress management for infertile patients was conducted by Dr Nirmal Bhasin at her centre at Chandigarh. It was attended by about 16 patients.

OCTOBER - An enlightening talk was given by Dr G.K. Bedi at Patiala on the topic of UNDERSTANDING INFERTILITY. This forum was for all the doctors in various fields of practice and also attended by the gynaecs.

Ppdate on Thyroid in Pre-pregnancy and Pregnancy was held. Talks by expert Endocrinologists of the Tricity was given. About 60 doctors attended the CME.

Dr SK Gupta
Chairperson



Dr Neha Priyadarshini
Secretary

JHARKHAND

Travelling SEMINAR of Jharkhand ISAR well attended by more than 100 specialists from all over the state. It was organised at Hotel Ramada, Jamshedpur on 17th November 2019. The speakers were Dr Gautam Khastgir, Dr Pratibha Singh and Dr Maninder Ahuja. Panel moderated by Dr Neha Priyadarshini (Secretary, Jharkhand ISAR).

Dr Manju Khurana
Chairperson

Dr. Manisha Mehta
Secretary

HARYANA

HCOISAR organised the following events:
CME at Bhiwani: In the month of June a CME was organised at Distt Bhiwani in which around 45 Gynaecologitsts and infertility specialists were present.A vast discussion was done on Endometriosis.
World Environment Day Celebrations: On 5th of June,The World Environment Day was celebrated with great enthusiasm all over Haryana. The HCOISAR members from different cities managed to perform different activities to make the society aware of the environmental changes. Trees were planted on large scale in every district. Cultural programs and skits were performed to give people the message to save the environment. At some places campaigns were initiated to stop polythene use. Jute bags were distributed and people were made aware not to use polythene bags. Poster making competitions were held at some places showing environmental changes and about the solutions to deal with the problem.
Annual Congress Of HCOISAR: On 11th of August, annual congress of HCOISAR was organised at Hisar. Around 200 delegates from all over Haryana attended the CME. National President of ISAR, Dr Jaideep Malhotra was the Chief Guest of the event. She delivered a Valuable talk on PCOD. MLA of Distt Hisar Mr Kamal Gupta was the Guest of Honour. He took keen interesst to know about HCOISAR and its activites. Many important issues that an infertility specialist must know about were taken up and talks were delivered by the experts.The queries were discussed well. We got 3 credit hours for the CME. Dr Ved Beniwal from MCI attended the conference. Dr Jaideep Malhotra gave a message to public through press: how stress was affecting fertility among couples. The CME was concluded with an IUI workshop. It turned out to be a successful congress.

PUNJAB

Dr PS Bakshi
Chairperson

Dr Jasmine Kaur Dahiya
Secretary

TRAVELLING ISAR SEMINAR 2019-20
ISAR Punjab Chapter

0n 10th August 2019 a scientific session was held as the ISAR traveling seminar on “The Ovaries: Understanding ovulation, Luteal Phase and Impact of Environment " .The meeting started with Flag Hoisting by the Chairperson and a Welcome address. Lamp Lighting was done by all the executive members of the Punjab Chapter. There were 2 Speakers Dr Sanjay Makwana and Dr Jasmine Dahyia. This was followed by a panel discussion on "Difficult cases in day to day practise”.Discussion was very interesting and eminent IVF consultants from all over Punjab were panelists. The meeting was attended by 110 participants and the speakers felicitated. The meeting ended with interesting discussions on ovulation Induction and Endocrine disrupter chemicals (EDCs). The vote of Thanks was by the Sun Pharma group who helped organize the meeting.

IUI WORKSHOP AND HANDS ON TRAINING
ISAR Punjab Chapter & NOVA IVI Fertility

On 25th August 2019 an IUI workshop with Hands on Training was organized at Nova IVI Fertility center and the meeting was accredited with CME hours by the Punjab Medical Council. The welcome address the Punjab Chairperson Dr P S Bakshi was followed by 3 lectures for 45 mins each discussing the causes, Investigations and treatment of male and female Infertility. This was followed by an Embryology discourse on “Improving results in IUI". This was followed by an interesting discussion and case presentation followed by Lunch and then Hands on for all the present Clinicians. Dr Kavita Bhatti From CMC&H Ludhiana was the guest of honor. The workshop was conducted by Dr Jasmine Dahyia Clinical Director Nova Jalandhar.The meeting was attended by 16 Participants.

A HEALTHY BODY MEANS A HEALTHY MIND

DR. HIMANSHU ROY
M.B.B.S (Hons) - MD
Chief Consultant
Srijan Fertility Clinic, Patna

As we get involved in clinical practice, we tend to start losing perspective of good health. Studies and admission to medical deselect us from the group of people who give more time to exercise as a part of their lives. Added to this is a relative sedentary lifestyle and family pressure with increasing age which has additional toil on our physical and mental health. These are few of the main reasons to buckle up and do not let these factors harm us. As we get older we have added responsibilities and expectations from everyone around us. It's not fair to tell our patients to keep in shape for their various diseases if we ourselves are not. Similarly an agitated mind will prevent us from taking the right decisions and make the workplace and home far from condusive.

My father was very keen that we look after ourselves in all the ways. Going for morning walks doing pooja, having regular exercise and games in evening as a routine was his way of doing this. In high school I joined NCC, karate class and gymming as we grew up seeing Bruce Lee, Rambo, Rocky movies. Bull Worker was the only gym equipment that was available. All this stopped once admission to the medical college happened. Anatomy and physiology were the new challenges and looking after health was not a priority. Though facilities for sports were available in college and hostel, they were used only for a week or two during the annual games. A whole decade passed like this and then we find ourselves struggling to make our careers. We get a wakeup call when we realise none of our clothes are fitting us anymore or fall ill.

Restarting exercise at middle age becomes a big challenge. Without proper guidance, sudden exertion can lead to ligament injuries which again puts to rest all fitness aspirations and years pass by till we want to again restart. We gradually acquire chronic illnesses like hypertension, diabetes or cardiac diseases and further limit our physical activities. The hardest part is to cut inches off our belly. Suddenly we feel ashamed looking and comparing our new and old pics.

It's very important to start exercise with proper guidance to avoid serious injuries. Exercise could be a mix of cardio, yoga, weight training, stretching and various outdoor and indoor games, All these activities should be built up gradually. Variations in the routine prevents it from getting boring.

Dieting can be really tough to continue for long. Various fancy diet plans are now available and trying one of them can be a good idea. I found Keto diet the most useful as you really don't have to avoid food but only change the ingredients. It is also gratifying to see weight loss from the first week itself.

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Susten VT 200

Natural Micronised Progesterone Vaginal Insert Tablet

Effervescent technology: Vaginal administration

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Ensures secretory & decidual transformation of endometrium[1]

Strong immunomodulatory effect prevents embryo rejection[1]

Enhances uterine quiescence[1]

Ensures therapeutic benefits in prevention and treatment of threatened miscarriage, recurrent miscarriage and preterm birth[1]

1. Czyk A et al. Gynecol Endocrinol 2017 Jun; 33(6): 421-424

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

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