Prof. Abha Majumdar

Director, Center of IVF and Human Reproduction
Sir Ganga Ram Hospital, New Delhi, INDIA

President's Medal for best medical graduate of year1970-75
Award from DMA on Dr. B.C Roy's birthday: outstanding contribution to medicine,1999
Vikas Ratan Award by Nations economic development & growth society 2002
Chitsa Ratan Award by International Study Circle in 2007
Life time Medical excellence award Obs & Gyne by Hippocrates foundation 2014
Abdul Kalam gold medal by Global Economic Progress & Research Association 2015
Rashtriya Gaurav Gold Medal award October 2017 by GEPRA
Distinguished teacher of excellence award for PG medical education by ANBAI & NBE doctors day on 5th Sept 2017 **and Inspiring Gynecologist of India** by the Economic Times on the same date in 2018

Course director for post doctoral **Fellowship in Reproductive Medicine** by NBE, since 2007, IFS since 2014, ISAR 2014 and by FOGSI for basic & advanced infertility training since 2008.
Member of Editorial board of '**IVF Worldwide',** peer reviewer for '**Journal of Human Reproductive Sciences',** Member of advisory board for '**Journal of Fertility Science & Research'** and consultant advisor for queries to NDTV.com
Field of interest: Infertility, ART, Reproductive endocrinology, Endoscopic surgery for pelvic resurrection and ART.

DR. ABHA MAJUMDAR

MBBS, MS, FICS
Director & Head of IVF Department
IVF Sir Ganga Ram Hospital

Expertise

Infertility, assisted reproductive techniques, reproductive endocrinology, endoscopic surgery for pelvic resurrection.

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SGRH
IVF SIR GANGARAM HOSPITAL

Smart stimulation of ovary to fit the budget

Prof Abha Majumdar

Director and Head

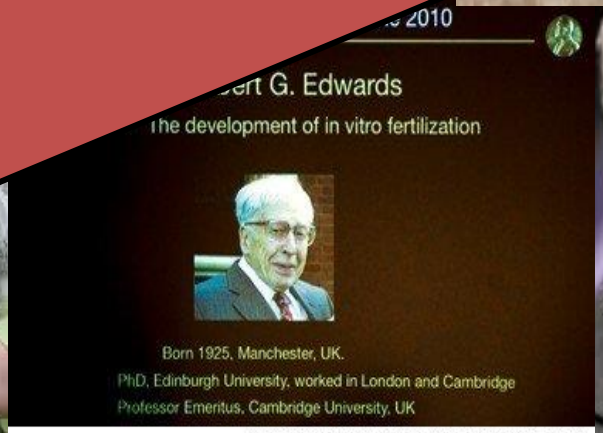
Centre of IVF and Human Reproduction

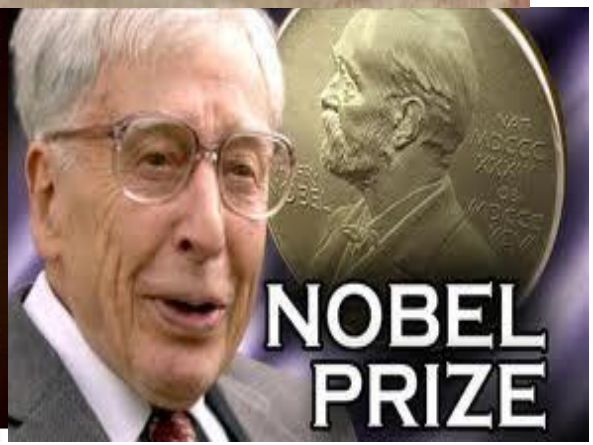
Sir Ganga Ram Hospital

New Delhi

Nobel Prize winner: The work of British physiologist [Robert G. Edwards] waited longest to be recognized. His award for medicine comes 32 years after he figured out how to create the beginnings of human life outside the uterus through in vitro fertilization.

Single oocyte Single embryo Single baby





Jonathan Nackstrand, AFP/Getty Images

IVF started to develop fast with the aim of maximizing pregnancy rates per cycle

COH for h**igher number of oocytes, thus more embryos**

- Use of un-physiological high doses of gonadotropins with time consuming protocols
- Higher costs, more office visit's,
- More tests and patient discomfort
- Higher risk of OHSS
- Very high risk of multiple gestation

Rapid progression of protocols and technology

This magic wheel had to slow down

Definition of success in IVF started shifting from pregnancy rate per cycle towards achieving healthy singleton child without complications per started cycle

For achieving this aim the first change had to be in stimulation protocols with the aim of:

- Less oocytes
- less cost
- less pain /stress
- Less complications
- Obtaining a good oocyte / embryo/ implantation rate
- Good pregnancy rates

Further progression of technology aimed at minimizing complication rat… maintainin… pregn…

Careful individualized COH

Progression of technology

Conventional stimulation protocols

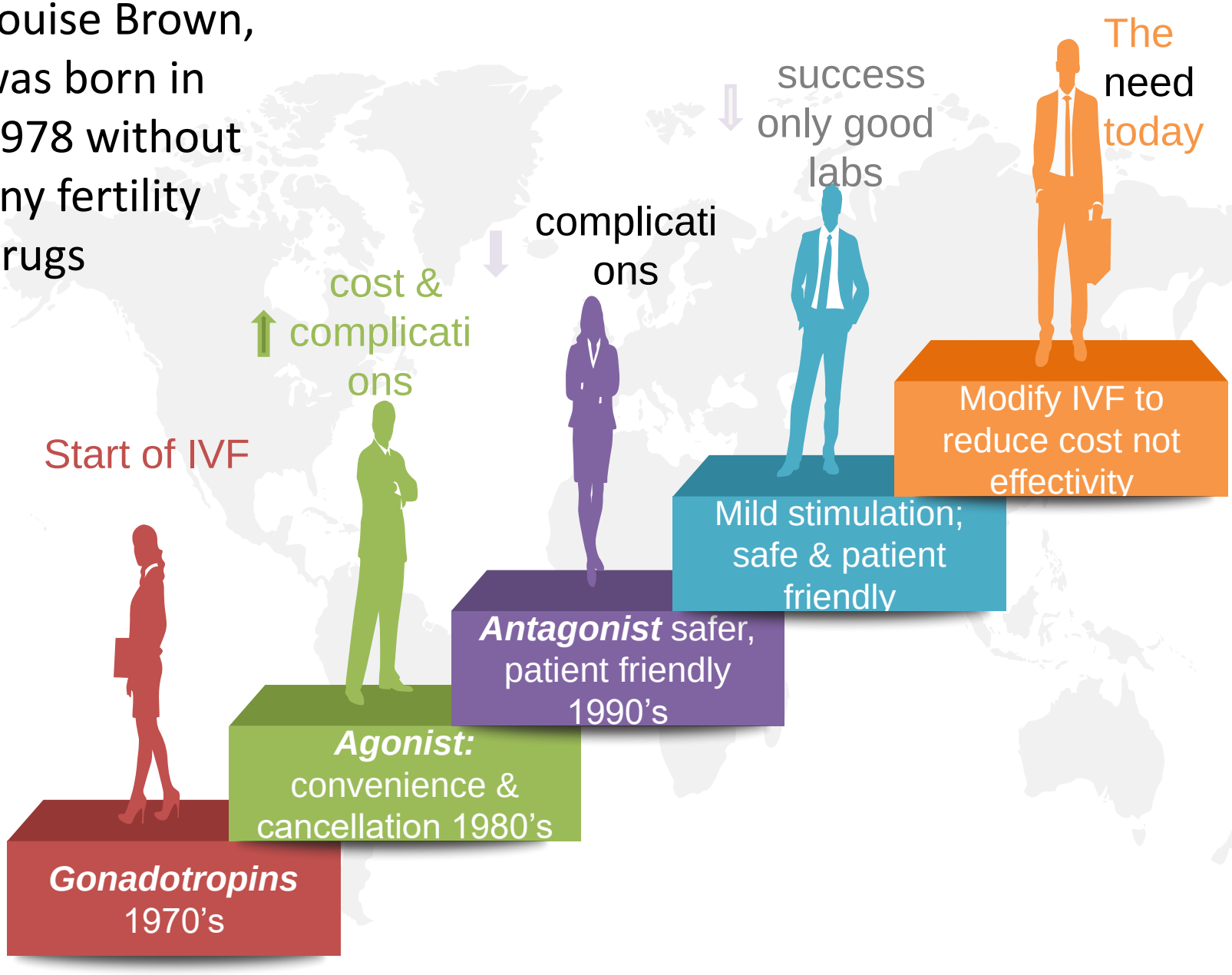
Conventional regimes	Aims at >8 oocytes but high complication OHSS

Milder stimulation protocols

Mild stimulation regimes	Aims at < 8 oocytes but needs very good lab conditions

Individualized stimulation protocols

Individualized COS (iCOS)	Best live birth rate with low complication rate; OHSS


Louise Brown, was born in 1978 without any fertility drugs
Start of IVF
cost & complicati ons
complicati ons
success only good labs
The need today
Gonadotropins 1970's
Agonist: convenience & cancellation 1980's
Antagonist safer, patient friendly 1990's
Mild stimulation; safe & patient friendly
Modify IVF to reduce cost not effectivity

Individualized ovarian stimulation will depend upon:

Type of response expected

Age

Weight

Ovarian reserve test

Hormonal imbalance

Hypo-gonadotropic hypo-gonadism)

Underlying pathology for IVF

Severe endometriosis

Male factor

Oocyte donor

Low cost IVF to fit all pockets

Time constraints of patient

Oncologic/thrombotic needs

Fertility preservation

Identifying response

Hyper responder

- Underlying PCOS
- Thin built
- Age < 30
- FSH < 8miu/ml
- AMH> 25pmol/l
- AFC>12
- Previous hyper response

Poor responder

- Regular or shortening cycles
- Obese
- Age >37
- FSH > 12miu/ml
- AMH<5pmol/l
- AFC < 6
- Previous poor response

Individualized ovarian stimulation will depend upon:

Type of response expected

- Age
- Weight
- Ovarian reserve test
- Previous response to

Hormonal imbalance

- PCOS/LH hyper-secretion
- Hypo-gonadotropic hypo-gonadism)

Underlying pathology for IVF

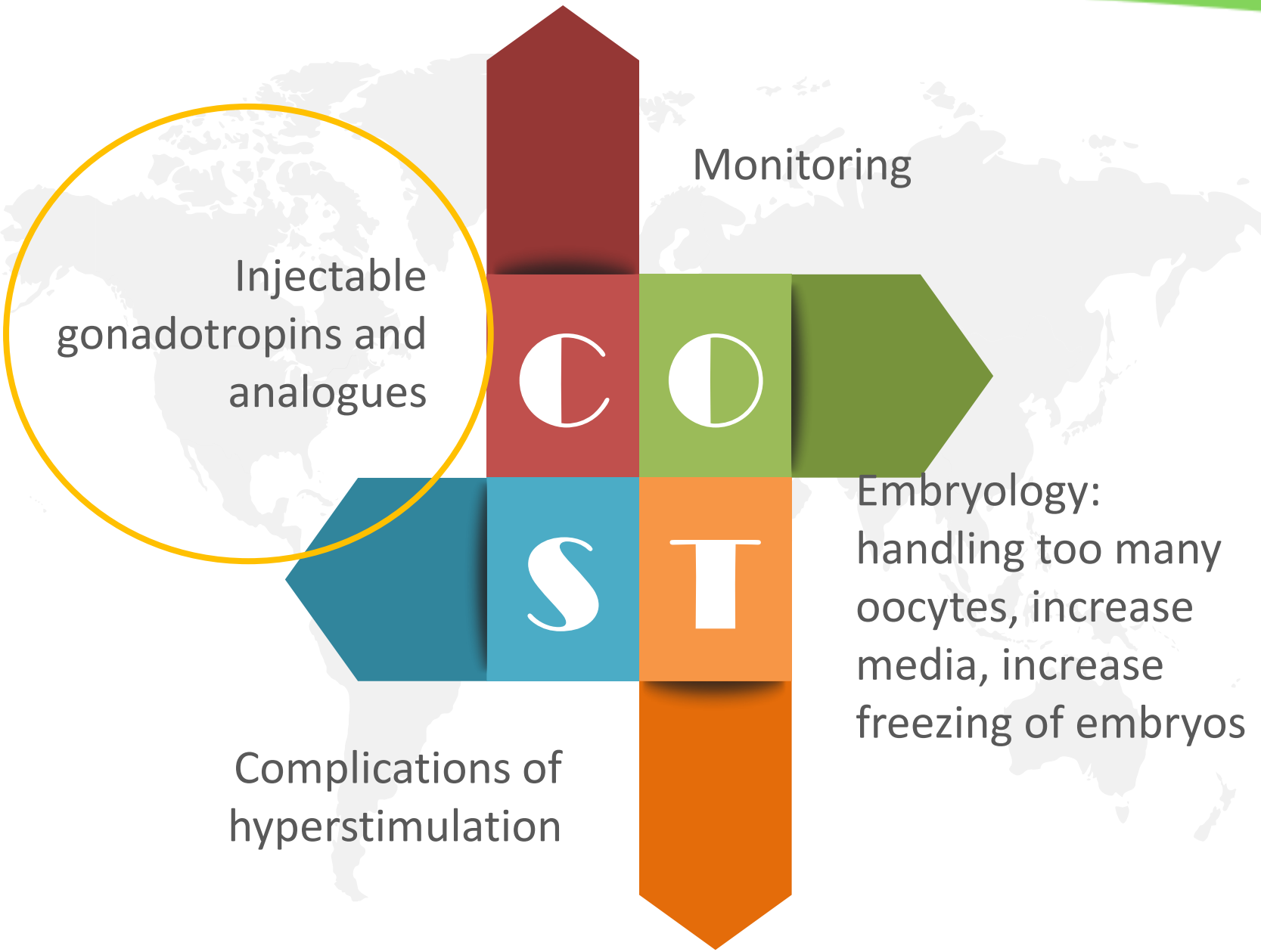
- Severe endometriosis
- Male factor
- Oocyte donor

Low cost IVF to fit all pockets

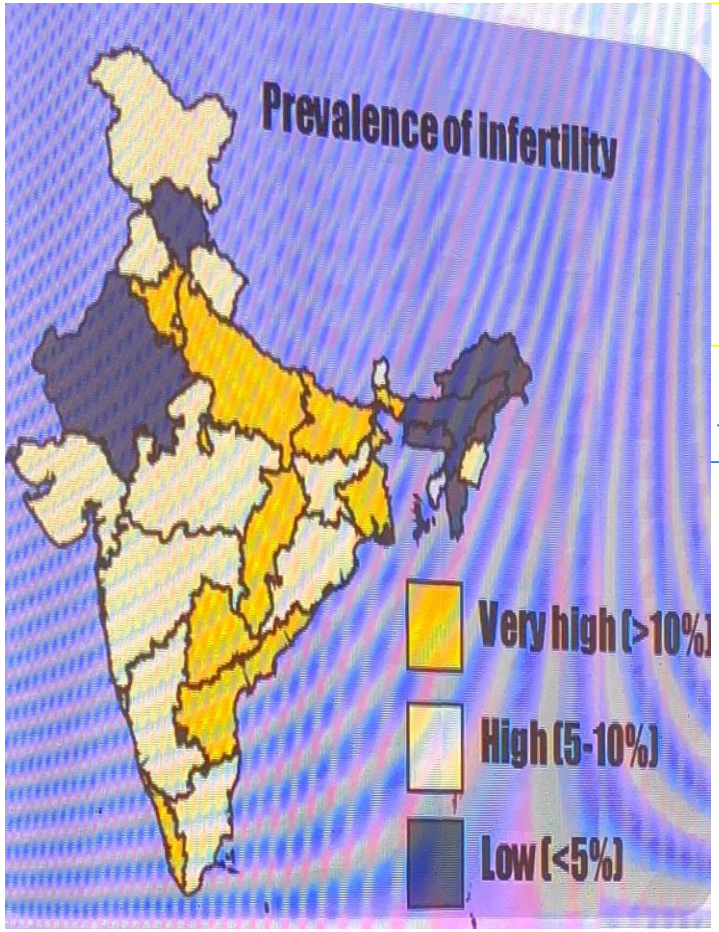
Time constraints of patient

Oncologic/thrombotic needs

Fertility preservation


Monitoring
Injectable gonadotropins and analogues
C
O
S
T
Embryology: handling too many oocytes, increase media, increase freezing of embryos
Complications of hyperstimulation

Infertility is an epidemic in India



≈ 4.2% Indian population suffer from infertility

≈ 1% of infertile couples seek IVF

≈ 0.05% india's total populatio n seeks IVF

We are doing **1 lac** cycles a year

But we need **93.3 lac** cycles a year

Source: EY 2015 report, ETPrime analysis

Low cost IVF to fit all pockets

In order to give some chance of pregnancy to infertile couples who simply cannot afford conventional IVF-ET with injectable drugs and the consequent cost of complications, we will have to bring in IVF-ET with low cost drugs and minimal injections.

This will not only decrease the total cost of the procedure, but will be taken up by more needy couples even though the success rates may appear compromised.

Natural cycle IVF (spontaneous ovulation)

1. No stimulation (oral medications or gonadotropins)
2. hCG trigger pre oocyte retrieval
3. No anaesthesia nor anaesthetist (I/V medicine for pain relief -1 or 2 follicles)
4. No luteal support

The basic techniques of oocyte retrieval, insemination, embryo culture, embryo transfer, and pregnancy testing after embryo transfer are very similar to those used in conventional IVF-ET.

Very good lab performance to enable 10 to 15% pregnancy rates.
Cost of IVF lab charges 50 to 66% lower (consumables & procedural)
Clinicians charges lower by 50 to 66% to sustain such programs

J Reprod Infertil. 2012 Jul-Sep; 13(3): 123. PMCID: PMC3719356

Low Success Rate of ART, an Illusion, a Reality or Simply a Too High Expectation?

Mohammad Reza Sadeghi, Editor-in-chief

Assisted reproductive technologies have spread worldwide to help infertile couples but access to these advanced treatments is of varying degrees in different countries. Access to infertility treatment is very limited and insurance coverage of these treatments is insufficient in developing, underdeveloped and low-income countries.

Why do we need ovarian stimulation?

Human Reproduction, Vol.31, No.10 pp. 2261–2267, 2016
Advanced Access publication on September 2, 2016 doi:10.1093/humrep/dew184

human reproduction ORIGINAL ARTICLE *Infertility*

Live birth and perinatal outcomes following stimulated and unstimulated IVF: analysis of over two decades of a nationwide data

Sesh Kamal Sunkara[1,*], Antonio LaMarca[2], Nikolaos P. Polyzos[3], Paul T. Seed[4], and Yakoub Khalaf[5]

Data from Human Fertilisation and Embryology Authority (HFEA) 1991 to 2011

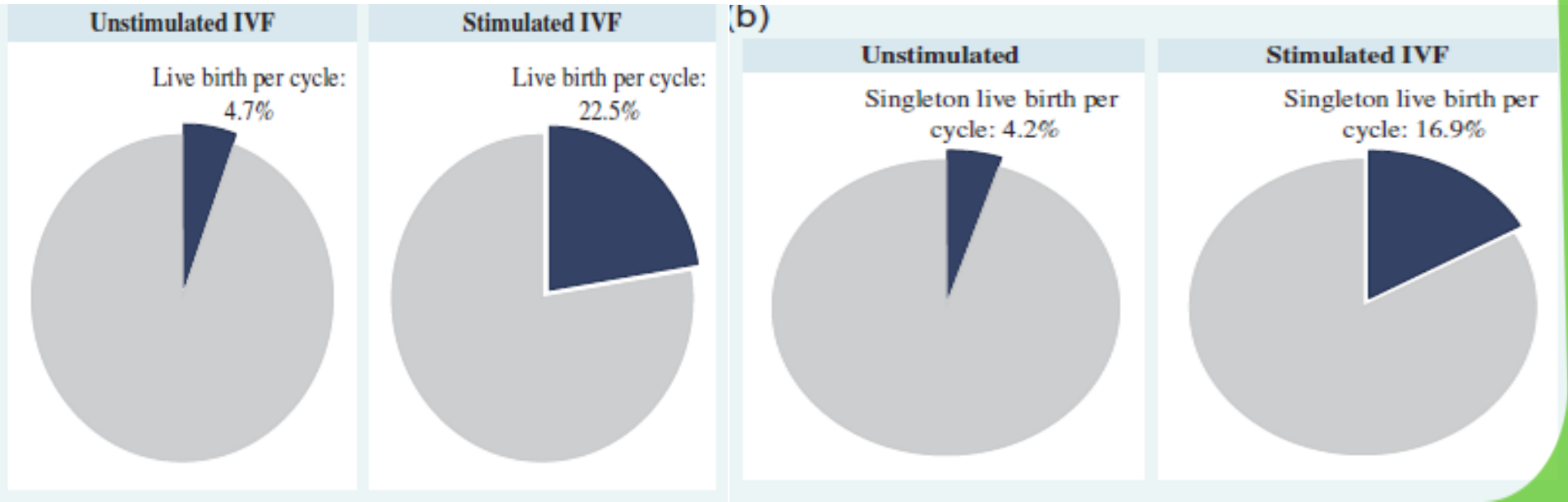
5,91,003 fresh IVF ± ICSI cycles

- 5,84,835 stimulated IVF cycles
- 6,168 unstimulated IVF cycles

Chances of no oocytes retrieved

- 44.2% - unstimulated cycles
- 7.1% - stimulated cycles

- To achieve live birth
  - 3.5 times more unstimulated IVF cycles required compared to stimulated IVF
- To achieve one singleton live birth
  - 2.9 times more unstimulated IVF cycles required compared to stimulated IVF.
- TTP shorter with stimulated IVF cycle



There are several slightly different ways in which IVF-ET can be performed with limited use of injectable gonadotropins in combination to oral drugs for enhancing ovulation as well as controlling spontaneous LH surge.

There are no universally agreed upon definitions to describe minimal stimulation protocols for IVF.

Minimal stimulation low cost protocols

Advantages

Inexpensive oral clomiphene followed by low dose gonadotropin and hCG trigger or just the hCG trigger shot alone.

- fewer injections,
- fewer days of monitoring,
- Less exposure to medications to developing eggs and the developing endometrium.

Who benefits

- Low responders who do not recruit many follicles even with full stimulation,
- High responders who are at a markedly increased risk of ovarian hyperstimulation syndrome,
- Patients who are not interested in embryo cryopreservation
- Women who want to limit the number of eggs to be fertilized, for ethical or religious reasons

Minimal stimulation IVF-ET SART

Oral low cost drugs to replace use of analogues to prevent LH surge:

1. **CC: day 3 to trigger**
2. **Progestogen: day 3 to trigger**

Use of oral low cost drugs to potentiate stimulation of gonadotropins:

1. **CC for first 5 days**
2. **Letrozole for first 5 days**

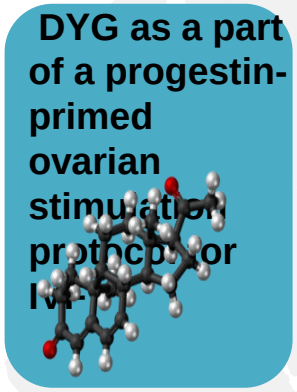
- Lower gonadotropin
- Less monitoring
- Lower lab. consumption
- Lower complications

Counter balanced by

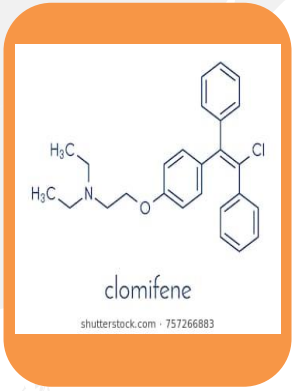
Need to vitrify all embryos and transfer them in subsequent natural cycles if analogues not used

ALTERNATIVE PROTOCOLS ESPECIALLY LOW COST FOR POOR OR NORMAL RESPONDERS

Kato O protocol

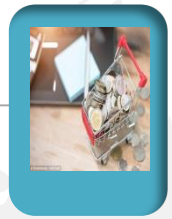


PPOS



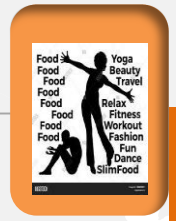
Clomiphene

Obtain a few high quality eggs, avoid risks of OHSS, reduce cost of drugs & number of injections.



CC 50 mgs from day3, till hCG trigger + FSH 150 iu on day 8 every alternate day.

approach to circumvent cost but maintain



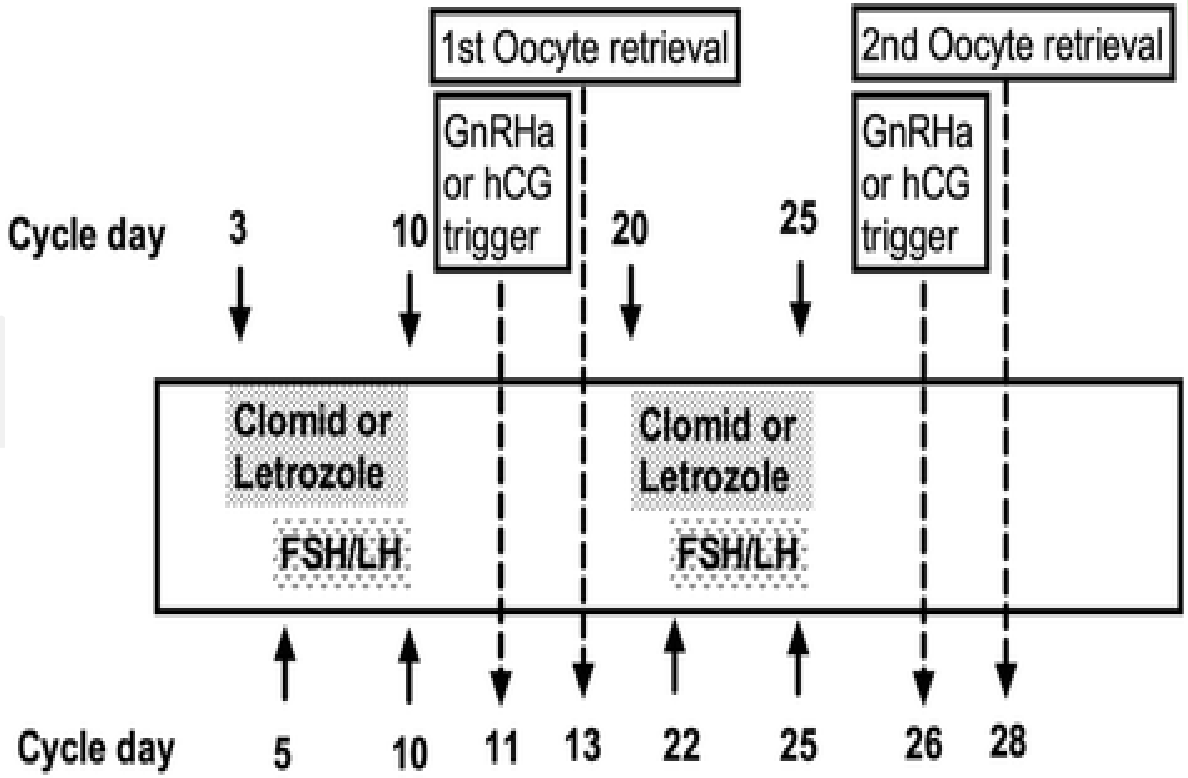
stimulate good number of follicles and block LH

Japanese Minimal Stimulation Protocol
Teramato S, Kato O
43,433 cycles
OR=83%, CR=64%, mean no of oocyte=2.2 and LBR=11.1%

Shanghai protocol

Dual stimulation
Follicular & luteal stimulation with GnRHa trigger in first stimulation

Follicular versus luteal phase ovarian stimulation during the same menstrual cycle (DuoStim) in a reduced ovarian reserve population results in a similar euploid blastocyst formation rate: new insight in ovarian reserve exploitation



Clomiphene citrate

[PDF] Use of clomiphene to prevent premature luteinizing hormone surge ...
www.ejmanager.com/mnstemps/89/89-1460112205.pdf?t=1464877999
by S Bhandari - 2017 - Cited by 2 - Related articles
Jun 1, 2016 - considerably, the ideal method to **prevent** premature luteinizing hormone ... use of antagonist. Keywords: **Clomiphene** citrate, **LH surge**, **In vitro fertilization**, Ovarian stimulation ... the **cost** was bore by the institute. The oocyte ...

Use of clomiphene to prevent premature luteinizing hormone surge ...
www.ijrcog.org/index.php/ijrcog/article/view/1255
by S Bhandari - 2017 - Cited by 2 - Related articles
Use of **clomiphene** to **prevent** premature **luteinizing hormone surge** during controlled ... **Clomiphene** citrate, **LH surge**, **In vitro fertilization**, Ovarian stimulation ... to the Standard Long Stimulation Protocol with a Significant Reduction in **Cost**.

Use of clomiphene-based stimulation protocol in oocyte donors: A ...
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5070397/
by A Singh - 2016 - Cited by 2 - Related articles
Clomiphene by its antiestrogen effect on the pituitary helps ovarian stimulation by releasing FSH; at the same time, it **prevents** the release of LH and thus **prevents** premature **LH surge** which can cause premature ovulation. This property of **clomiphene** can be used in **IVF** stimulation protocol.
Abstract · INTRODUCTION · MATERIALS AND METHODS · RESULTS

Clomiphene citrate in LH surge suppression for women undergoing ...
https://www.sciencedirect.com/science/article/pii/S1110569017303060
by NM Shams-Eldeen - 2018 - Related articles
Feb 1, 2018 - Keywords. **Clomiphene**. **COS**. **LH surge**. Premature luteinization ..... in order to **prevent** **LH surge** without affecting the **IVF**/ICSI cycle outcomes.

Journal List › J Hum Reprod Sci › v.8(3); Jul-Sep 2015 › PMC4601172

J Hum Reprod Sci. 2015 Jul-Sep; 8(3): 142–145.
doi: [10.4103/0974-1208.165151]
PMCID: PMC4601172
PMID: 26538856
Clomiphene based ovarian stimulation in a commercial donor program
Shruti Gupta, Ruma Satwik, Abha Majumdar, Shweta Mittal, and Neeti Tiwari

PPOS

Stimulation with gonadotropin with didrogesterone 10mg/d to stop LH surge from day 2 daily till trigger

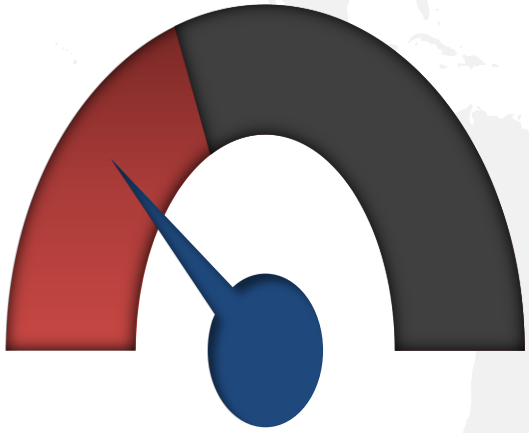
Hum Reprod. 2018 Feb 1;33(2):229-237. doi: 10.1093/humrep/dex367.

New application of dydrogesterone as a part of a progestin-primed ovarian stimulation protocol for IVF: a randomized controlled trial including 516 first IVF/ICSI cycles.

Yu S, Long H, Chang HY, Liu Y, Gao H, Zhu J, Quan X, Lyu Q, Kuang Y, Ai A

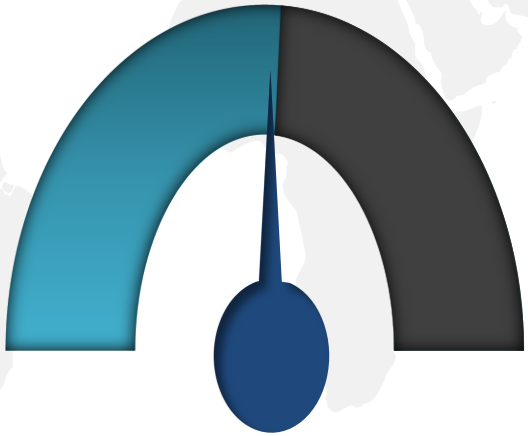
To make IVF affordable to all

Compromised results even with good labs



Mild stimulation protocols

Good results less cost least complications



Development of newer COS protocols

Good results but increase cost and complications

Conventional iCOS

Thank you