Dr. Abha Majumdar
Director, Center of IVF and Human Reproduction
Sir Ganga Ram Hospital,
New Delhi, INDIA

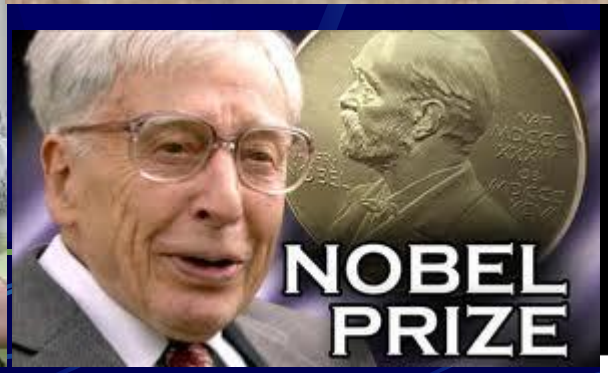
Awarded **Presidents Medal** for Best Medical Graduate 1975
Felicitated by **Dr. B.C Roy's prestigious award** in 1999.
Awarded **Bharat Vikas Ratan Award** by nations Economic Development and Growth Society 2002,
Chiktsa Ratan Award a certificate of excellence in Medical Science by the International Study Circle, 2007
Felicitated by S.N.Medical College for outstanding contribution to specialty in 2008
Appointed by National Board to award **Fellowship in Reproductive Medicine** 2007
Attached to Sir Ganga Ram Hospital, New Delhi since 1987. At present Director of 'Centre of IVF and Human Reproduction' of SGRH. This hospital provides comprehensive infertility services under one roof as one of the most prestigious and largest center of Northern India.

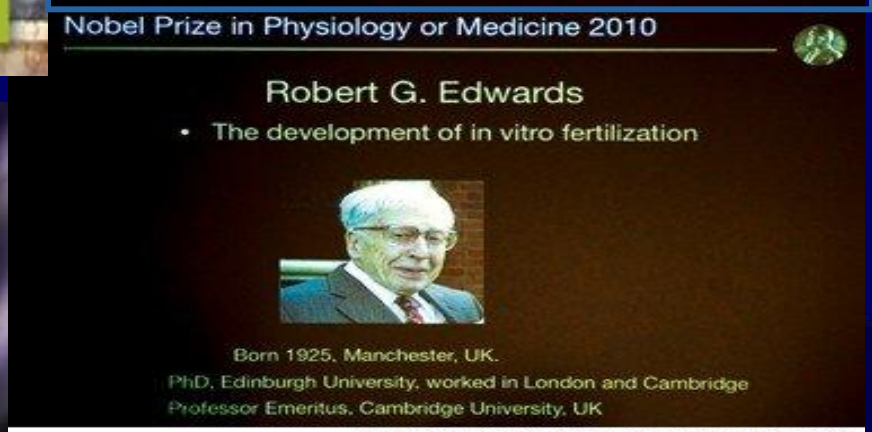
Optimum Ovarian stimulation for IVF....?

Dr. Abha Majumdar
Center IVF and Human Reproduction
Sir Ganga Ram Hospital New Delhi
INDIA

Single oocyte
Single embryo
Single baby

Of this year's Nobel Prize winners, 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.





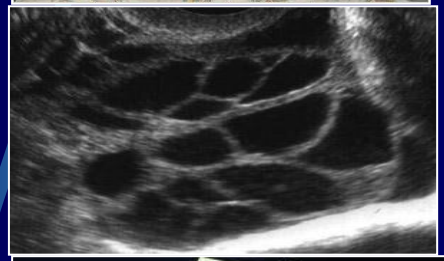
Jonathan Nackstrand, AFP/Getty Images

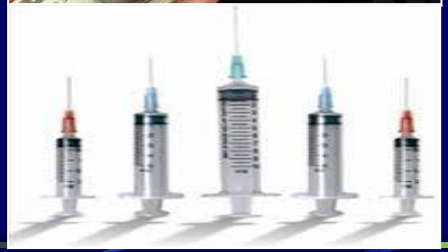
IVF started to develop fast with the aim of maximizing pregnancy rates per cycle

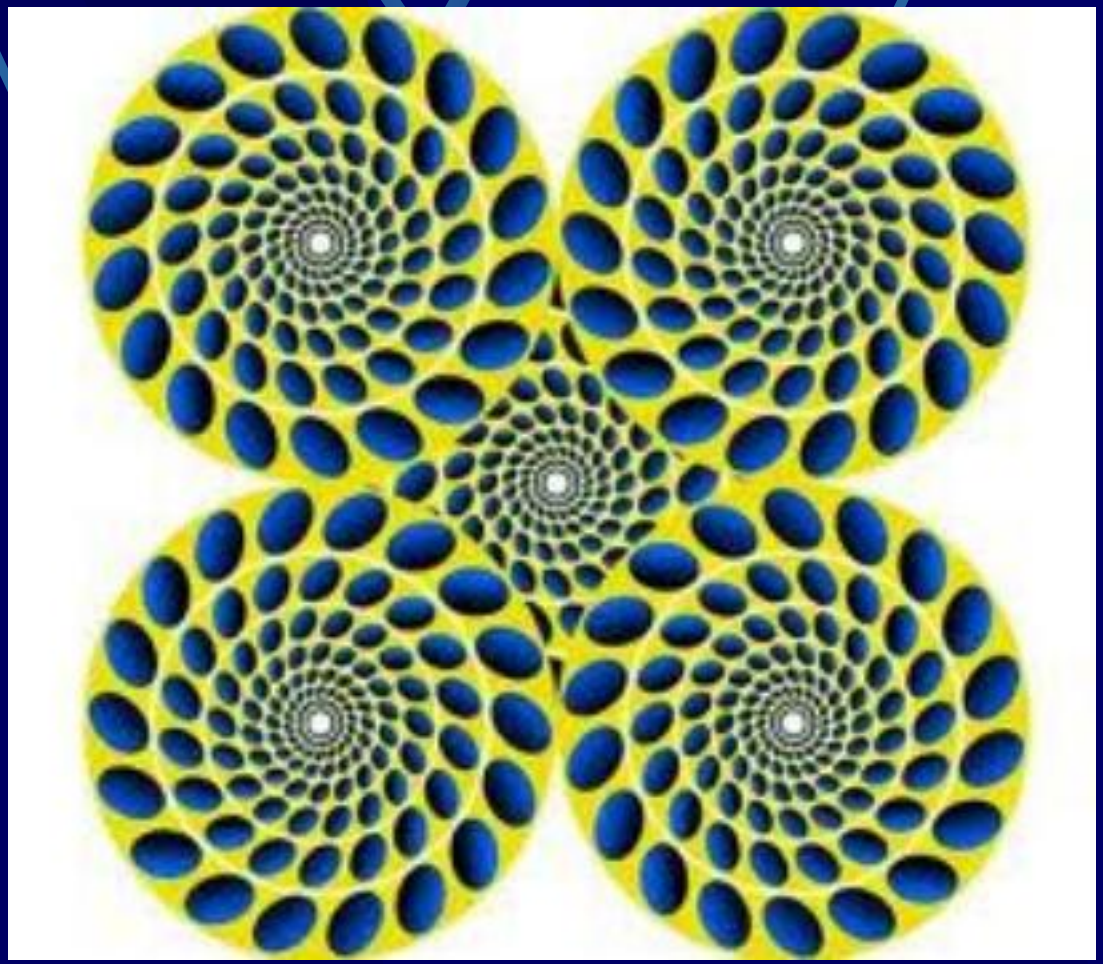
- Higher number of oocytes and thus more embryos
- Use of unphysiological high doses of gonadotropins
- Time consuming protocols
- Higher costs
- Patient discomfort
- Higher risk of OHSS
- Very high risk of multiple gestation

Rapid progression of protocols and technology

This magic wheel had to slow down







Look at this wheel closely and it shall start spinning

Definition of success in IVF is shifting from pregnancy rate per cycle towards achieving healthy singleton child per started course of treatment.

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

- less stress
- less cost
- less pain
- Less complications
- Obtaining a good embryo & implantation rate

Further progression of technology to minimize complications rate yet maintaining optimal pregnancy rates

What is optimum ovarian stimulation in IVF?

- A cycle which gives the couple the best chance of pregnancy with lowest or no risk of OHSS and/or multiple pregnancy (*what ever the underlying diagnosis may be for which the couple has to undergo IVF)*

Optimization of stimulation protocols depend upon:

Type of response expected

Ovarian reserve test

Previous response to stimulation

Age

Weight

Underlying diagnosis

Severe endometriosis

Male factor

Oocyte donor

Hormonal imbalance

PCOS/LH hyper-secretion

Hypo-gonadotropic hypo-gonadism)

Time constraints of patient for treatment

Preferences for milder stimulation

Type of response expected

Ovarian reserve test (ORT)

Previous response to stimulation

Age

Weight

Identifying response

Hyper responder

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

Normal responder

- Regular cycles
- Normal built
- Age < 37
- FSH <12miu/ml
- AMH 10 to 25pmol/l

Poor responder

- Regular cycles
- Obese
- Age >37
- FSH > 12miu/ml
- AMH<3pmol/l
- Previous poor response to stimulation

Optimizing treatment protocols for normal responder

- Long protocol (GnRH agonist down regulation followed by FSH 75 to 200 iu/day)

- Antagonist protocol *(flexible / fixed protocol)*

- Short agonist protocol *(pre treatment with ocp 14 days* ***or*** *antagonist 0.25mg/day* ***or*** *estradiol valerate 4 m /day from day 25 of previous cycle)*

Optimizing treatment protocols for high responder

- Antagonist protocol (fixed dose regime preferred)
- Long protocol
- Short agonist protocol
- Minimal stimulation protocols

In all protocols low dose FSH 75 -150 IU/day

Optimizing treatment protocols for poor responder

- GnRH agonist *'conventional dose'* with FSH 150 to 300IU
  - *Stop protocol*
  - GnRH agonist *'mini dose'*
- Antagonist protocol with flexible regime
  - *Higher dose of FSH 150 to 300units per day*
  - *Adding LH or HMG to FSH*
- Short agonist protocol
- Flare agonist with antagonist flexible protocol

The Cochrane database of systemic reviews 2008

Treatment protocols for poor responders

6 comparison groups (9 trials analyzed)

- Stop protocol vs. conventional GnRHa long protocol
- GnRH antagonist vs. conventional GnRHa long protocol
- Bromocriptine rebound protocol vs. GnRHa long protocol
- GnRHa short protocol vs. GnRHa long protocol
- GnRH antagonist vs. GnRHa short protocol
- Low dose flare protocol vs. spontaneous natural

The Cochrane database of systemic reviews 2008

Results in poor responders

- More oocytes in *antagonist* protocol with lower doses of gonadotropins vs *long protocol:* no difference in pregnancy, abortion or cancellation rate.
- No difference in cancellation rate short vs antagonist protocol (OR 2.04, 95%CI 0.81 to 5.1 p value 0.13)
- Short had significantly higher no. of oocytes than antagonist protocol
- Cancellation rate lowest in *Long Protocol* compared to *short and flare*

Summary of results in poor responders

There is insufficient evidence to support the routine use of any particular intervention for ovarian stimulation or adjuvant therapy.

Due to low incidence of poor ovarian response the evaluation of interventions proposed have been performed in single, under-powered studies, which might not have allowed the detection of the true effect of the intervention.
More robust data from good quality RCT's with relevant outcomes are needed.

Hormonal imbalance

PCOS/LH hyper-secretion

Hypo-gonadotropic hypo-gonadism

PCOS with LH hypersecretion

- Down regulation with *GnRH agonist* followed by stimulation with gonadotropins (FSH)
- Endogenous gonadotropin inhibition with *GnRH antagonist* & stimulation with gonadotropins (FSH)

Pre treatment
oral contraceptives for 2 to 3 months
Drilling

PCOS (without LH hypersecretion)

- Preferably antagonist protocol
- Lower starting doses of FSH (75 to 100 units)
- Rec FSH pen with smaller dosing options
- GnRH agonist trigger if hyper-stimulation of ovaries
- ET planned in same cycle: progesterone with estrogen support after trigger betters PR. (1 bolus hCG 1500 IU 35 hrs after GnRH trigger *Penarrubia et al., 1998; Emperaire et al., 2004* **or 3** doses of 500 UI of hCG on day 1,4 and 7 post OPU *Castillo et al., 2010* recommended).

Hypogonadotropic hypogonadism

- Step up regime with HMG is the ideal treatment
- LH control not required no need of agonist or antagonist
- Luteal support mandatory with hCG as well as progesterone.

Pretreatment with estrogen and progesterone cyclically for 6 to 9 months till the mid cycle endometrium appears ideal for implantation.

Underlying diagnosis

Severe endometriosis

Male factor

Oocyte donor

Severe endometriosis

Meta analysis ESHRE 2005

Administration of GnRH agonists for 3–6 months prior to IVF in patients with endometriosis increases clinical PR (4 fold) and the live BR significantly (9 fold).

Cochrane data base systemic review 2006

Long term down regulation for 60 to 90 days before IVF for women with endometriosis is better than long protocol: 3 RCTs with 165 women **(Evidence level 1b)**

Live BR/ woman OR 9.19: Clinical PR: OR 4.28

ESHRE guidelines for endometriosis 2008

GnRH agonist for 3 to 6 months before IVF should be considered in women with endometriosis: increases odds of clinical PR fourfold.

Male factor infertility

- Antagonist protocol
- Milder stimulation regimes
- hCG trigger

Optimum stimulation for Oocyte donors

Donors for oocytes undergoing ovarian stimulation

Improved donor satisfaction is likely to improve donor recruitment and retention

Minimizing trips to the clinic; using protocols that limit the number of I/M injections; reducing risk of OHSS; reimbursing for expenses such as lost work, travel, and child care; treating them with respect and appreciation; and informing them about outcome.

A qualitative follow-up study of women's experiences with oocyte donation; A.L. Kalfoglou; *Hum. Reprod. (2000) 15 (4): 798-805.*

Gonadotropin-releasing hormone agonists versus antagonists for controlled ovarian hyperstimulation in oocyte donors: a systematic review and meta-analysis

Daniel Bodri; Fertility and Sterility, Volume 95, Issue 1 , Pages 164-169, January 2011

No significant differences observed after donor stimulation with GnRH agonist or antagonist protocols on number of retrieved oocytes or ongoing pregnancy rate

Given the high efficacy and safety of the GnRH-antagonist protocol triggered with a GnRH agonist, monitoring of E2 not necessary. USG monitoring is enough for follow up of donor cycles. Antagonist protocol also uses lesser days of injections.

J.C. Castillo et al, Reprod BioMed Online, Nov. 2011

GnRH agonist trigger constitutes a safe treatment option for egg-donors. No compromise on embryo quality and risk of OHSS reduces considerably in antagonist protocol with agonist trigger.

- *Anna Galindo, January 2009, Vol. 25, No. 1 , Pages 60-66*
- *A. Sismanoglu et al, J. Assist Reprod and Genetics, 26; 5, 251-256*
- *M Melo et al, ReprodBioMedOnline,19; 4, October 2009, 486–492*

Time constraints of patient for treatment

Preferences for milder stimulation

Milder Stimulation Regimes

The international society for Mild Approaches in Assisted Reproduction (ISMAAR) proposal on terminology for ovarian stimulation for IVF

- All responders (poor, normal and hyper)
- Oocyte Donors (no risk)
- Male factor IVF
- Women who come in mid follicular phase and have time constraints (want IVF within a week)

No margin for suboptimal laboratory performance

The ISMAAR proposal on terminology for ovarian stimulation for IVF

Table 2: Definitions

Terminology	Aim	Methodology
Natural cycle IVF	Single oocyte	No medication
Modified Natural cycle IVF	Single oocyte	hCG only GnRH antagonist and FSH/ HMG add-back
Mild IVF	2–7 oocytes	Low dose FSH/HMG, oral compounds and GnRH antagonist
Conventional IVF	≥8 oocytes	GnRH agonist or antagonist conventional FSH/HMG dose

The strength and weaknesses of milder stimulation after 10 years of experience?

Outcome of mild ovarian stimulation after 10 years of practice

Strength

- Reduced complexity, patient discomfort, risk & cost
- Beneficial effect on oocyte/ embryo quality
- Better implantation prospects
- Similar live birth rates per started treatment

Weakness

- Lower pregnancy rates / cycle
- Cost of medication still high
- Fewer embryos for freezing
- Difficult programming
- ***Less margin for suboptimal laboratory performance***

Fauser et al.Hum Rep ,Vol.25,no.11

Optimum ovarian stimulation in IVF would eventually mean?

- A cycle which gives the couple the best chance of pregnancy with lowest or no risk of OHSS and/or multiple pregnancy (*what ever the underlying diagnosis may be for which the couple has to undergo IVF)*

OVULATION INDUCTION IS NOT ONLY A SCIENCE BUT ALSO AN ART

JOY OF PARENT HOOD

Androgens in ovarian stimulation in poor responders

- Use of androgen supplements in poor responders could enhance the ovarian response and reduce the need for excessive FSH dosage.

- Some studies have suggested that ***transdermal testesterone*** supplements provide a nominal 2.5mg/day delivery rate and enhance follicular development if given between days 1 and 5 of cycle

Massin N et al . Hum Rep 2006;21:1204-11

Androgens in ovarian stimulation in poor responders

- Short term ***DHEA*** supplementation prior to ART for 12 to 15 weeks in women with poor ovarian reserve may enhance ovarian function, improve oocyte yield and pregnancy rates. No data to support DHEA supplementation in all women undergoing ART

  Barad D et al. J Assist Reprod Genet 2007;24:629-34

- ***Aromatase inhibitors*** from day 1 to 5 reduces the total amount of FSH required in women undergoing ART. Use of AI use in ART remains off licencse.

Addition of growth hormone in poor responder?

Does Growth Hormone improve oocyte quality or numbers?

- GH and IGF-1 reduce apoptosis and improve health and proliferation of granulosa cells which are crucial to the nourishment of maturing oocyte

Bensomo E. Fertil Steril 2006; 85:474-80

- GH increases intra-ovarian IGF production, which stimulates follicular development, estrogen production and oocyte maturation

Adashi et al., 1985; Erickson et al., 1989; Yoshimara et al., 1996

Prediction of poor responder

- Age: 38 to 42 years
- S.FSH: Rising basal serum FSH levels >12miu/l
- S. Estradiol: High basal E2 levels with normal FSH
-
- FSH:LH ratio: 3:1 or more
- AMH levels below 3 pmol/L
- CC stimulation test with exaggerated FSH response

Prediction of high responder

- Underlining PCOS
- Thin built women
- Age: less than 30 years
- S.FSH: Basal serum FSH levels below 8 miu/l
- FSH:LH ratio: 1:3 or more
- AMH levels over 25 pmol/L

Role of addition of LH in stimulation regimes?

Which subgroups may benefit?

- Older women
- Poor responders
- Hypo-gonadotropic hypo-gonadic women
- PCOS (late follicular phase during coasting)

1.Marrs et al. Reprod Biomed Online 2004;8:175–182
2. Humaidan et al. Reprod Biomed Online 2004;8:635–643
3. De Placido et al. Clin Endocrinol (Oxf) 2004;60:637–643
4. Ferraretti et al. Fertil Steril 2004;82:1521–1526
5. Acevedo et al. Fertil Steril 2004;82:343–347
6. Cédrin-Durnerin et al. J Gynecol Obstet Biol Reprod (Paris) 2004;33:3S29–3S31
7. Sauer et al. Reprod Biomed Online 2004;9:487–493

Long acting gonadotropin

Corifollitropin α (long acting FSH preparation)

(Single injection able to initiate and sustain multiple follicular growth for 7 days)

- Can only be used in known normal responders
- RCT comparing corifollitropin α and rec-FSH in an antagonist cycle reported no difference in pregnancy rates

Devroey P et al Hum Rep2009;24:3063-72

Little experience of Corifollitropin**α** with agonist cycles