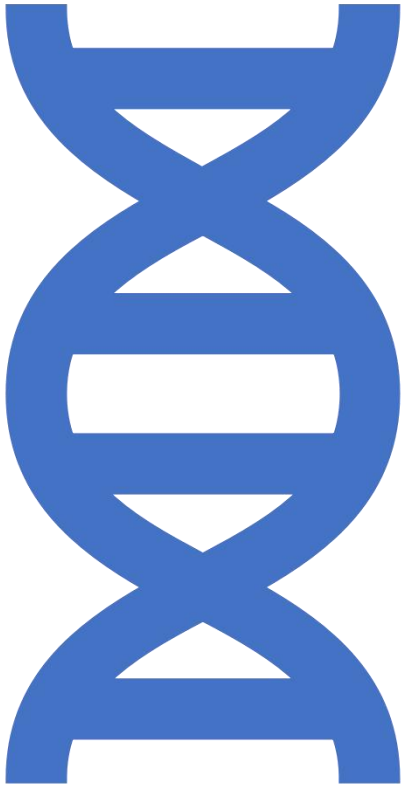
Prof. Abha Majumdar

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

President's Medal for best medical graduate of year1970-75
Life time Medical excellence award Obs & Gyne by Hippocrates foundation 2014
Abdul Kalam gold medal 2015 & **Rashtriya Gaurav Gold Medal award** 2017 by Global Economic Progress & Research Association.
Distinguished teacher of excellence award *for PG medical education by ANBAI & NBE 2017.*
Highest Merck Serono honor award in 2018.
Awarded at the Economic Times Health Care awards the ***"ICON of IVF of North India",*** *her team as the '****Best integrated national team of IVF****', & the most coveted award as the '****IVF National Champion of 2019'.***
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',** and member of advisory board for '**Journal of Fertility Science & Research'.**
Field of interest: Infertility, ART, Reproductive endocrinology, Endoscopic surgery for pelvic resurrection and ART.



Individualized embryo transfer

DR. ABHA MAJUMDAR

DIRECTOR & HEAD, CENTRE OF IVF AND HUMAN REPRODUCTION

SIR GANGA RAM HOSPITAL

NEW DELHI 21

Single oocyte
Single embryo
Single baby

Of this year's Nobel
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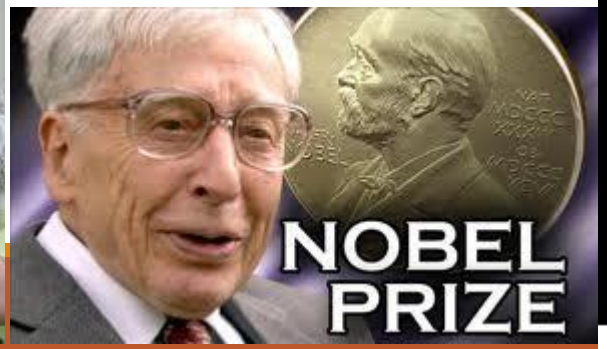
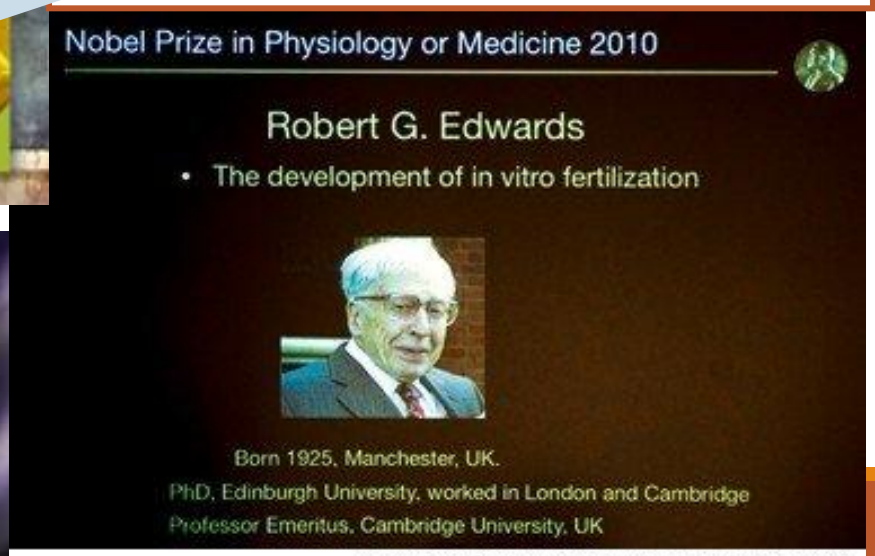
IVF was born in 1978 with the birth of Louise Brown





Jonathan Nackstrand, AFP/Getty Images

Progression of technology

Conventional stimulation protocols and fresh embryo transfer

Standard doses for all and fresh embryo transfer	Increased OHSS, high multiple pregnancy rates & lower implant and pregnancy rates

Individualized controlled ovarian stimulation

Tailored doses as per patient profile and freeze embryos if over stimulated	OHSS minimal, better implant and pregnancy rates & lower multiple pregnancies

Individualized embryo transfer

Individualize embryo transfer as per the woman's health and her implantation window	Safeguards woman's health with highest pregnancy rates

Conventional embryo transfer (CET):

OCR followed by one or multiple embryos transferred at any stage of development in COS fresh cycle with the aim to achieve early & highest pregnancy rates despite the health risks.

Individualized embryo transfer (IET):

Definite number of embryos (fresh or frozen) to transfer in a woman not only with the aim of achieving the highest chance of pregnancy but also to minimize the woman's health risks in all respects.

Conditions which warrant only single embryo transfer

- uterine malformations
- uterine surgery
- Previous obstetrical complications

Conditions which do not allow fresh embryo transfer

- Risk of OHSS
- Risk of progesterone elevation
- Inappropriate endometrium
- Medical condition peri COS

Conditions which warrant only frozen embryo transfer

- Non synchronized donor- recipient cycles
- PGT embryos
- RIF: displaced WOI
- Previous ectopic in IVF cycle

Conditions which warrant only single embryo transfer

Conditions which warrant only single embryo transfer

- Uterine malformations: unicornuate or bicornuate uterus
- uterine surgery: myomectomy adeno-myomectomy, previous hysterotomy
- Obstetrical complications:

  2nd trimester miscarriage or twin miscarried, cervical incompetance

  h/o severe PET or gestational diabetes
- I child present: request for 1 child from the couple

Conditions which do not allow fresh embryo transfer

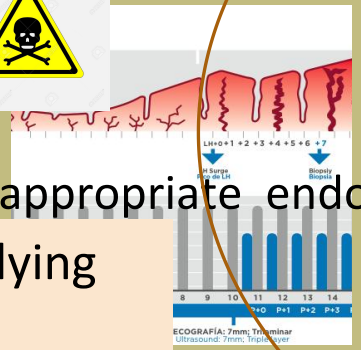
ALL INDICATIONS EITHER SAFEGUARD WOMAN'S HEALTH

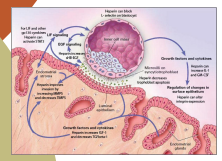
OR

OPTIMIZE CHANCES OF PREGNANCY

Conditions which do not allow fresh embryo transfer

Risk of OHSS





Inappropriate endometrium

Underlying PCOS
Pre-hCG high E2 levels

Stronger & longer stimulation for IVF

progesterone elevation

Thick or thin endometrium
Polyps, bleeding or fluid in cavity

Medical or surgical emergencies during COS

Can we reliably predict risk of OHSS

- Young less than 30 years
- Thin built
- Underlying PCOS
- High AMH >3.5ng/ml and AFC >22
- Previous history of OHSS
- High serum E2 IVF > 2500 pg OI >1200
- Multiple stimulated follicles > 20

OHSS-Free Clinic

by segmentation of IVF Treatment

IVF SIR GANGARAM HOSPITAL

STEP 1

Antagonist protocol

Patients friendly

- Fewer injection
- Shorter stimulation
- OHSS much lower
- Sam

STEP 2

GnRH agonist trigger

-LPD thus lower PR

-Aggressive luteal support if ET

-Cryo-preserve and subsequent transfer

STEP 3

Cryopreserve embryos

-PR higher

-OHSS ZERO

-Ethical issues of CP of embryos

Ovarian hyper-stimulation syndrome

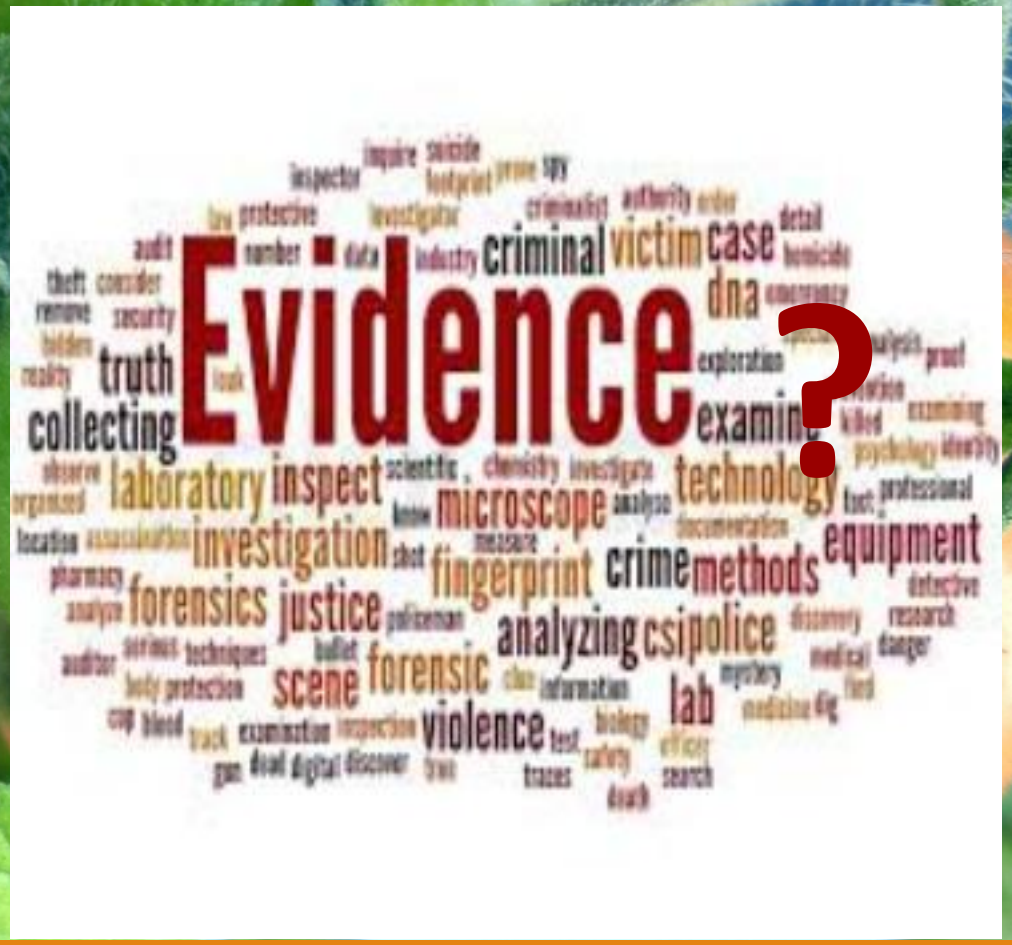
OHSS

A purely clinician[illegible]ed ***iatrogenic life threaten[illegible]*** condition occurs in absolute[illegible] *healthy and young* women desiring to have a child

No fresh transfer in COS cycle

Evidence is emerging which supports altered Endometrial Receptivity with progesterone elevation in late follicular phase in COS for IVF

Elevated serum P4 may be associated with diminished implantation and LBR in fresh embryo transfer cycles

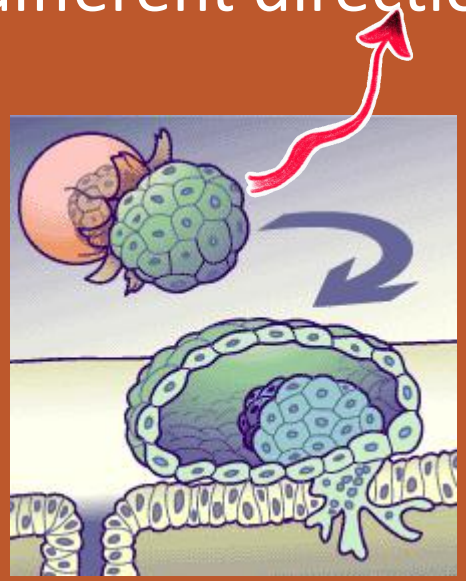


Progesterone elevation

Embryo &
Endometrium
are 2 different entities

and

can develop in 2
different directions.



With the
development
of IVF we
learnt

COS can render endometrium inappropriate for implantation while still generating perfect quality oocytes

The first proof of endometrium being independent of oocyte formation came into alive with the development of oocyte donation IVF program

Duo stim, luteal phase stimulation are examples of dissociation between oocyte/embryo formation without the endometrium being anywhere appropriate for implantation.

COS for IVF with progesterone being used instead of GnRH analoges to suppress LH and develop the endometrium at a later date was another example to prove this dissociation

Our concern

Premature rise of progesterone in late follicular phase with COS for IVF cycles is a frequent event

Cannot be prevented by use of GnRH analogues

Occurs with normal LH levels without premature luteinization, & is caused by ovarian overstimulation *(Lawrenz et al., 2016)*

Incidence up to 38% of all stimulated cycles, independent from the protocol used for stimulation

Several publications describe the negative impact of premature P elevation on the outcome of ART-treatments

Bosch E et al. Circulating P4 levels and ongoing pregnancy rates in COS cycles for IVF: analysis of over 4000 cycles. Hum Reprod 2010;.

Impact of high P4 levels on embryo implantation

- High progesterone exposure targets the endometrium causing its accelerated or dys-synchronous maturation confirmed by histology as well as gene expression profile in stimulated cycles. ***Labarta E et al,. A functional genomics analysis. Hum Reprod 2011;26:1813–25***

PREMATURE P ELEVATION—RESCUE STRATEGIES

- Administration of Corticosteroids
- Influence of agonist vs antagonist Stimulation Protocol in Case of Subtle P Elevation
- Type of Stimulation Medication and Stimulation Intensity
- Stimulation Duration (hCG delay by 1 vs 2 days)
- Timing of Embryo Transfer in Case of P Elevation (extending to blastocyst)
- Freeze-All Strategy and Cycle-Segmentation

Progesterone elevation

Reprod Biomed Online. 2017 Apr;34(4):422-428. doi: 10.1016/j.rbmo.2017.01.011. Epub 2017 Jan 24.

Effect of progesterone elevation in follicular phase of IVF-cycle

Lawrenz B[1], Fatemi HM[2]

Abstract;

Elevated peripheral P
endometriu
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en

This ***represent the critical threshold***, at which a negative effe ongoing pregnancy rate in fresh IVF cycles can be observed.

Days of exogenous progesterone exposure = embryo age

Do serum levels of progesterone also matter? (multiple routes high doses)

Would high dose of P4 also lead to displaced WOI in FET cycles??

HRT cycles for FET

advanced on day of oocyte

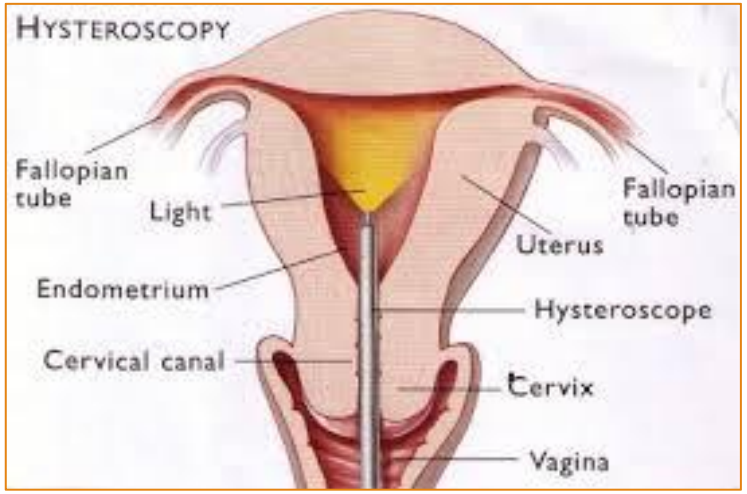
hCG trigger causing alteration in

on day of final oocyte maturation.

Endometrial defects seen during COS

- Very thick or thin endometrium during COS
- Sub-mucous myomas & polyps
- Bleeding with looss of endometrial thickness
- Fluid in endometrial cavity with connecting hydrosalapinx

Treat the defect medically or surgically before transfer



Freeze-All Strategy and Cycle-Segmentation

Freeze-all approach can be applied with cycle-segmentation and individualised ET in subsequent cycle.

Fatemi HM, Garcia-Velasco JA.. Fertil Steril 2015

ALERT.!

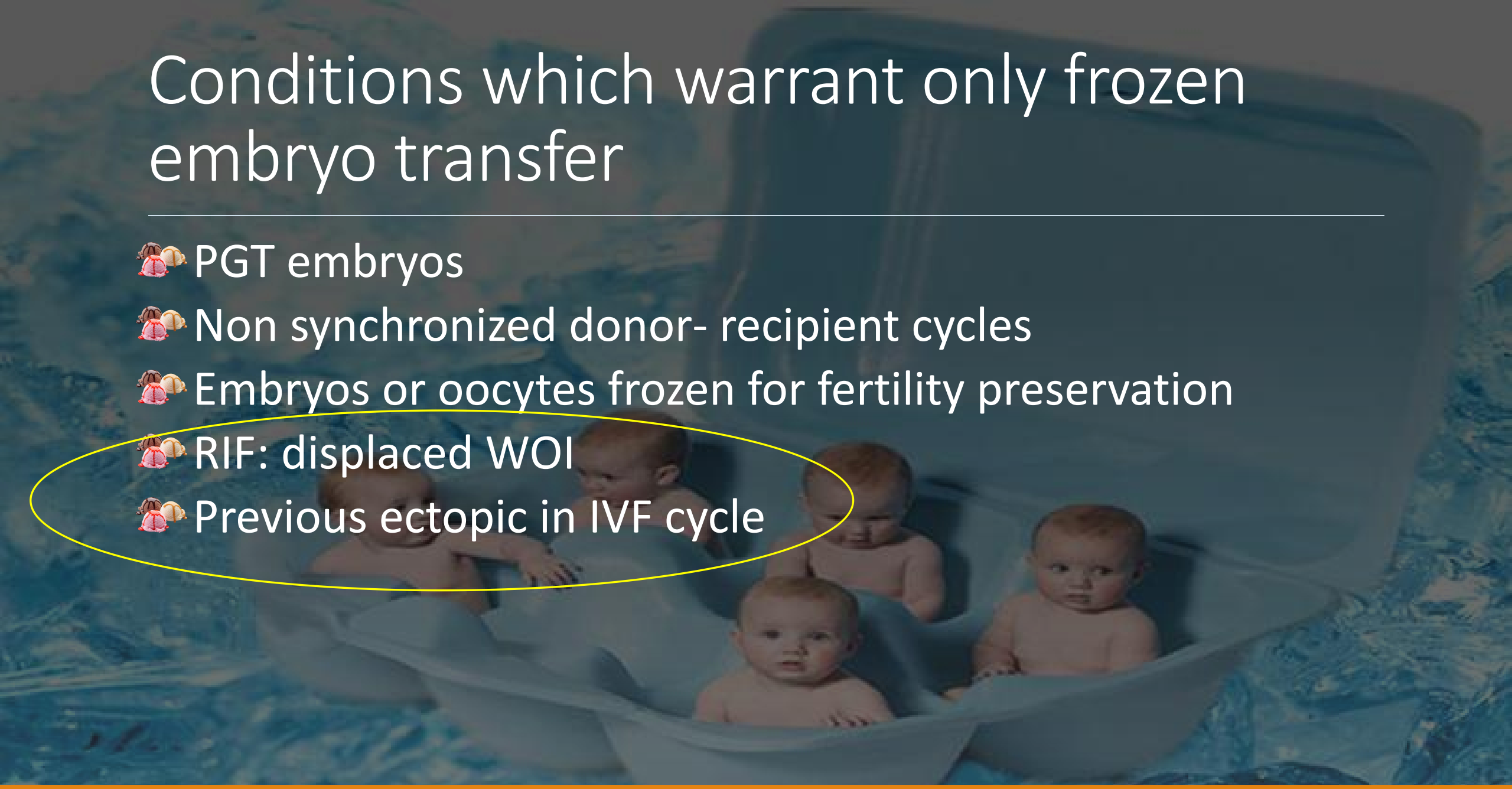
Freezing and thawing might induce epigenetic alterations in key genes and transcripts, such modifications might have long-term consequences for the child conceived after frozen thaw embryo replacement.

Kopeika J, Hum Reprod Update 2015

Conditions which warrant only frozen embryo transfer

Conditions which warrant only frozen embryo transfer

- PGT embryos
- Non synchronized donor- recipient cycles
- Embryos or oocytes frozen for fertility preservation
- RIF: displaced WOI
- Previous ectopic in IVF cycle



Recurrent Implantation failure and displaced window of implantation

RECURRENT IMPLANTATION FAILURE

- Failure to achieve a clinical pregnancy after transfer of at least 4 good-quality embryos in a minimum of 3 fresh or frozen cycles in a woman under the age of 40 years

C Coughlan et al., 2014 -

- More recently if 2 good morphology euploid embryos fail to implant it is considered as recurrent implantation failure

DISPLACED WINDOW OF IMPLANTATION

Window of implantation: Period of 2 to 3 days when endometrium becomes receptive for implantation of embryo. This results from the programmed sequential action of P4 on estrogen primed endometrium.

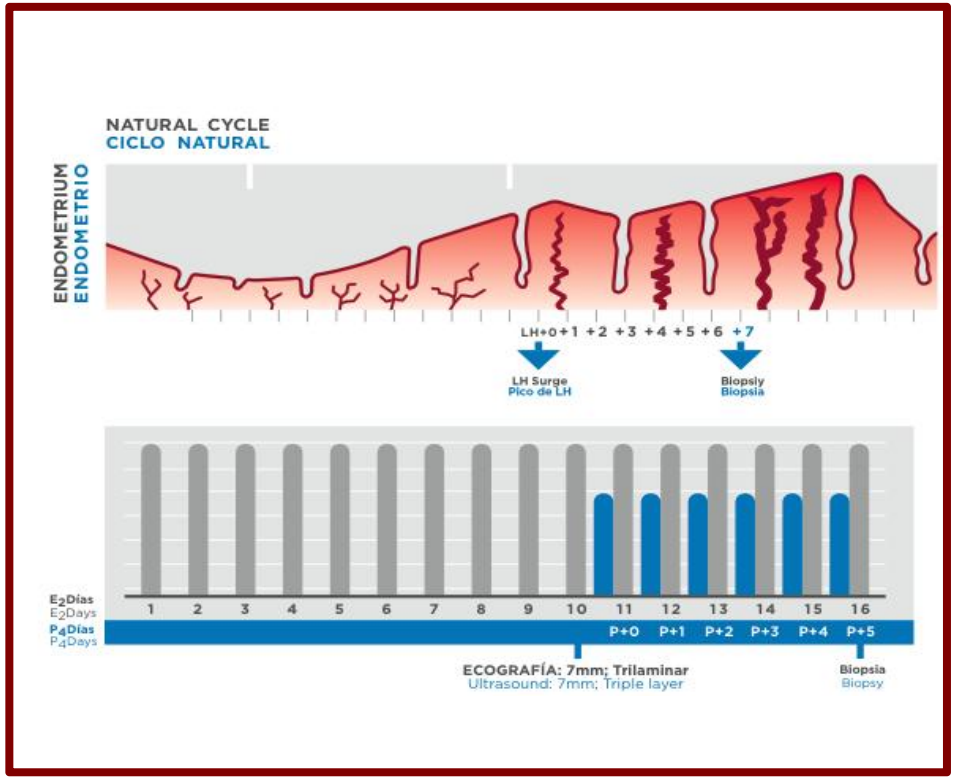
Displaced window of implantation: Presence of endometrial markers at an inappropriate time of cycle by the action of P4 on estradiol primed endometrium, leading to abnormal development of endometrium, preventing embryo implantation

EMBRYO

EMBRYO

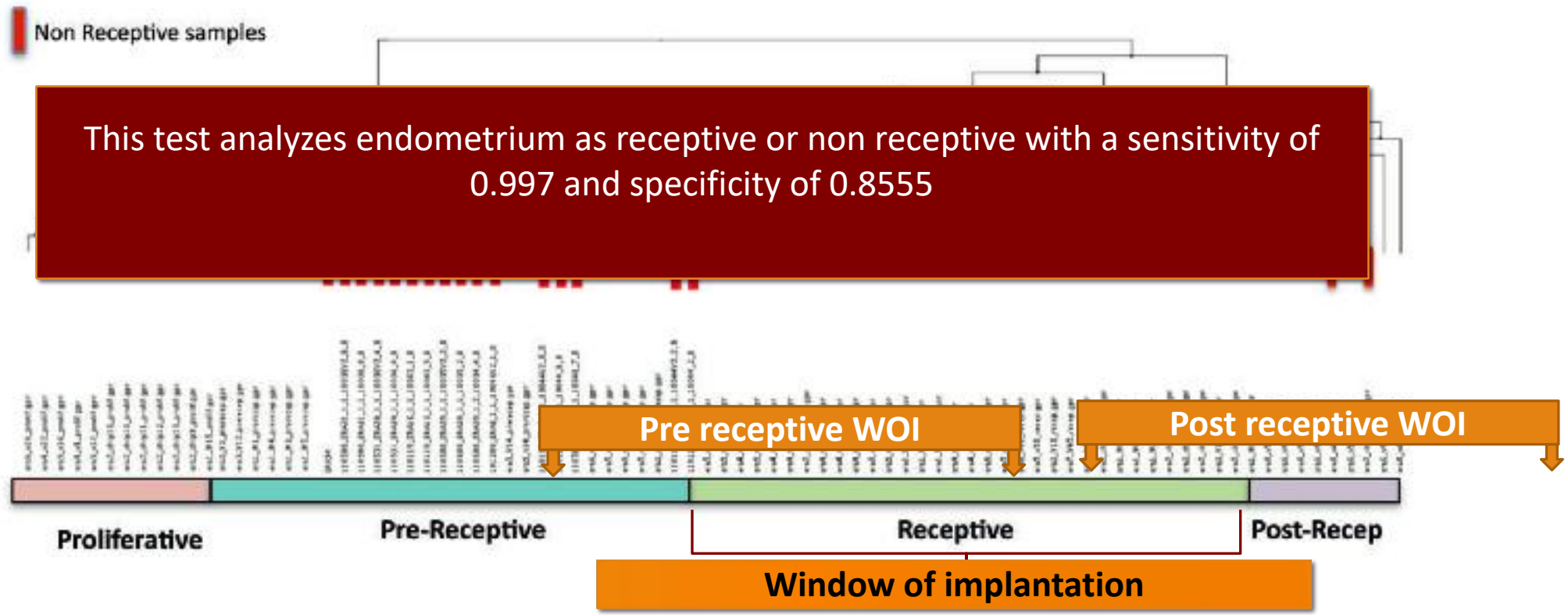
Genetic advancements to optimize Implantation

ERA is a microarray assay that quantifies the expression of 238 genes involved in endometrial receptivity

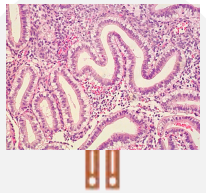


Endometrial receptivity array (ERA) is a personalized genetic test to diagnose the state of endometrial receptivity in the window of implantation.
Indicates the ideal time of WOI hence the days of progesterone exposure for embryo implantation in that particular HRT cycle

How is ERA report generated ?



Short comings of ERA



Cannot histologically date endometrium or identify pathological endometrium

Similar pregnancy rates in ERA performed and non performed group

Inconsistency in biopsy dates in natural cycle vs artificial cycle

WOI spans for 3 days, so how slight change in progesterone day change WOI

Previous ectopic in IVF cycle

Is frozen embryo transfer cycle associated with a significantly lower incidence of ectopic pregnancy? An analysis of more than 30,000 cycles

Bo Huang, Ph.D., Dan Hu, M.D., Kun Qian, Ph.D., Jihui Ai, Ph.D., Yufeng Li, Ph.D., Lei Jin, Ph.D., Guijin Zhu, M.D., Hanwang Zhang, Ph.D.*

Incidence of EP per clinical pregnancy was 4.62% for fresh transfer compared with 2.22% for frozen-thawed cycle group; (statistically significant).
fresh ET cycles had highest risk of EP, followed by day-3 embryo FET cycles; blastocyst FET cycles had lowest risk of EP, ALL differences statistically significant.
Frozen-thawed ET cycles were associated with a statistically significantly lower risk of EP when compared with fresh cycles.

Conclusion

Oocyte and embryo donation model was the first example of individualization of ET with donor & recipient being prepared simultaneously to synchronize OCR and ET.

The purpose of individualized ET is to safeguard the women's health on one side and optimize the chance of pregnancy on the other side.

Individualized ET took birth with the advent of successful vitrification of embryos.

The policy of freeze all and subsequent ET started as a strategy to prevent OHSS.

Segmentation of cycles has been extrapolated to numerous indications now such as presence of a polyp at OCR, thin or thick endometrium on day of ET, means to circumvent medical or surgical emergencies and be able to postpone ET in cases of progesterone rise on day of hCG during COS.

In true cases of RIF there is an option to investigate genetic endometrial markers and treat her appropriately before individualized ET to optimize success.

"Education is not the learning of facts, but the training of the mind to think."
-Albert Einstein