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More or less

&

which one is better

OVARIAN STIMULATION FOR IVF

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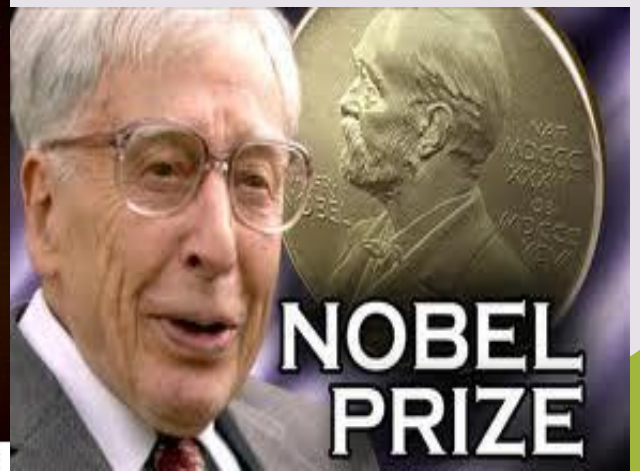
Nobel Prize winner: The work of British physiologist Robert G. Edwards waited longest to be recognized. His award for medicine comes 32 years after he figured out how to create the beginnings of human life outside the uterus through in vitro fertilization.

Single oocyte
Single embryo
Single baby

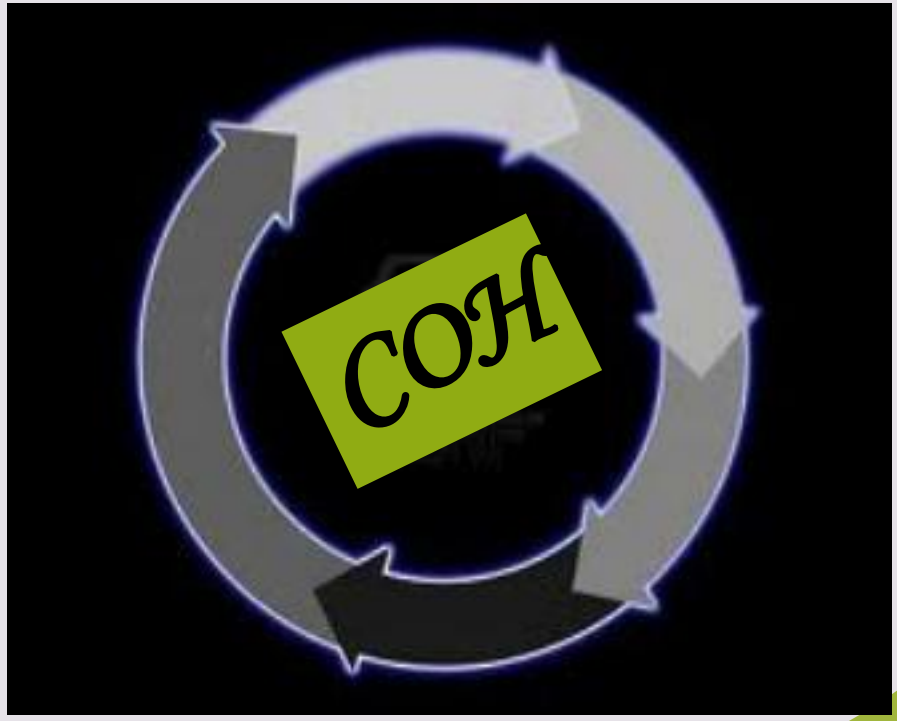


IVF started to develop fast with the aim of maximizing pregnancy rates per cycle

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

- Use of unphysiological high doses of gonadotropins
- Time consuming agonist long protocols
- Higher costs
- Patient discomfort
- Higher risk of OHSS
- Higher % multiple gestation

Rapid progression of protocols and technology



This magic wheel had to slow down

NATURAL CYCLE IVF

- no stimulation
- hCG trigger pre-oocyte retrieval
- no injections
- little monitoring
- no anaesthesia nor anaesthetist (I/V medicine for pain relief -1 or 2 follicles)
- no luteal support

MILD STIMULATION IVF(SART)

- inexpensive oral clomiphene followed by low dose gonadotropin
- hCG trigger
- fewer injections
- fewer days of monitoring,
- less exposure to medications to developing eggs and endometrium.

The basic techniques of oocyte retrieval, insemination, embryo culture, embryo transfer, were very similar to those used in conventional IVF-ET.

Very good lab performance to enable 10 to 15% pregnancy rates.

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]

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Data from HFEA) 1991 to 2011

591003 fresh IVF ± ICSI cycles

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

Chances of no oocytes retrieved

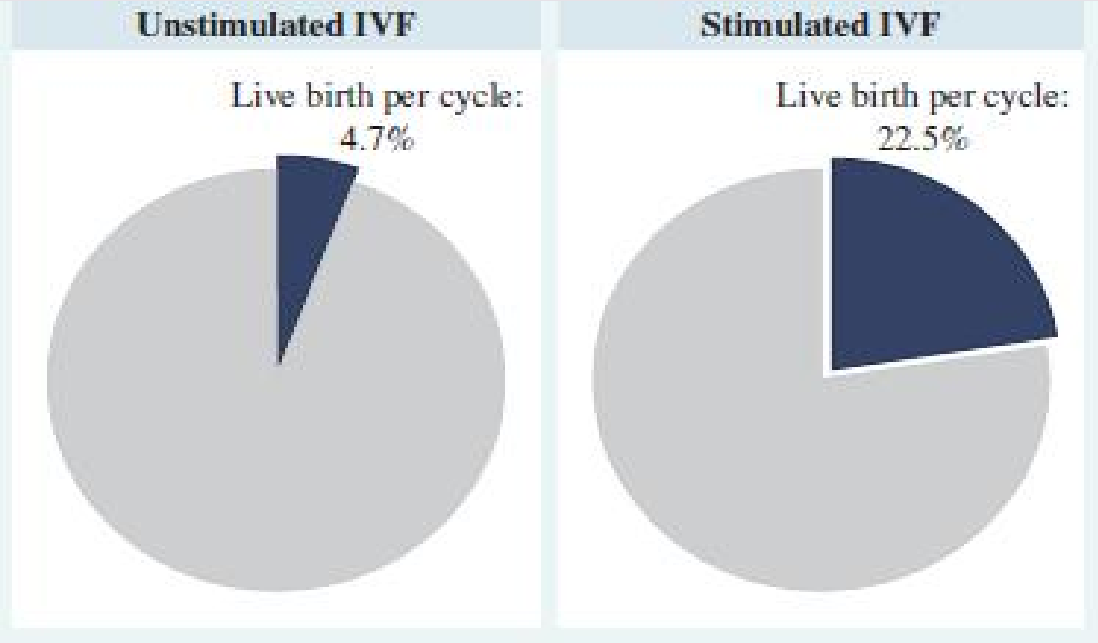
44.2% - unstimulated cycles

7.1% - stimulated cycles

To achieve live birth

- 3.5 times more unstimulated IVF cycles required compared to stimulated IVF

TTP shorter with stimulated IVF cycle



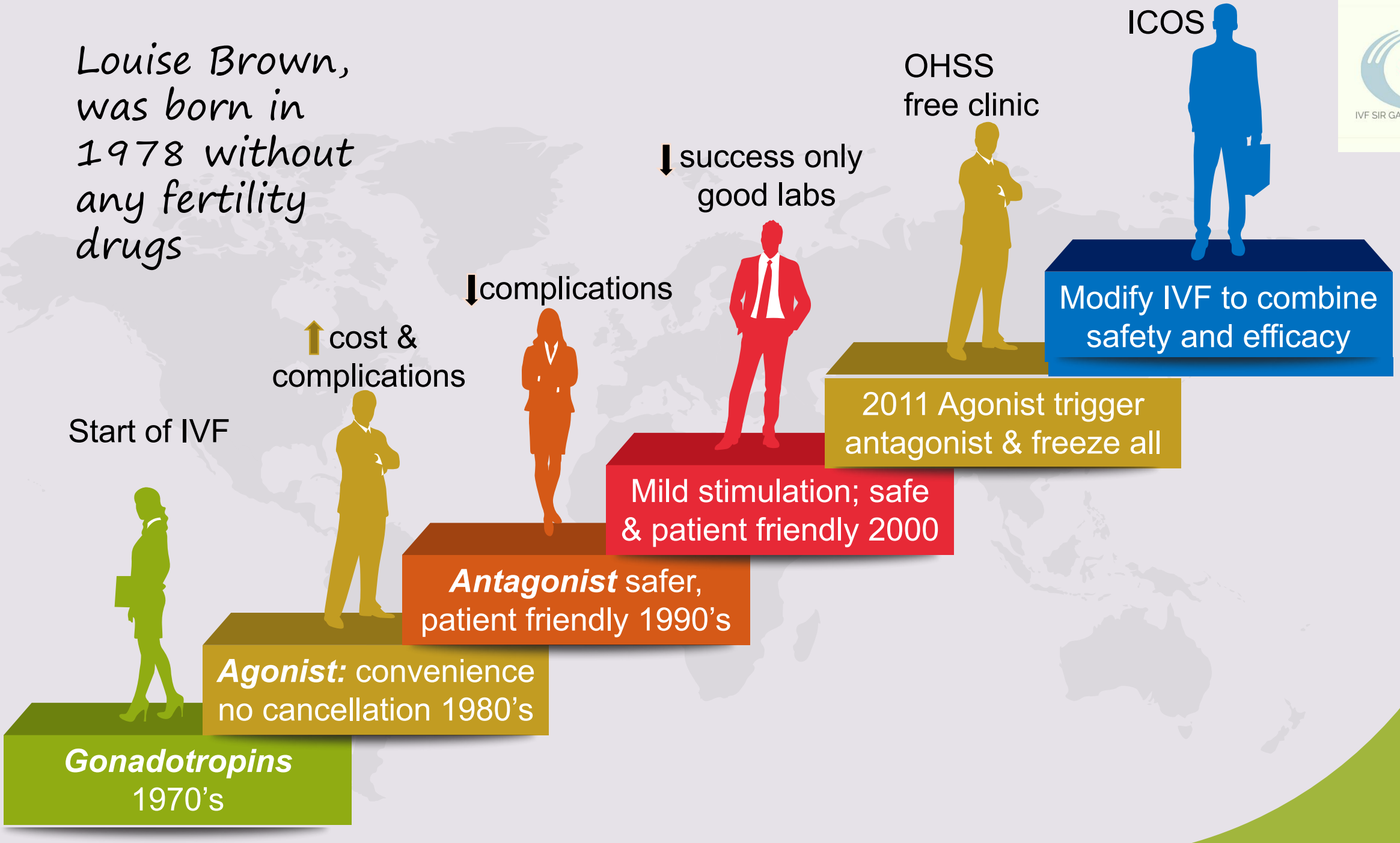
Definition of success in IVF started shifting from pregnancy rate per cycle towards achieving live birth rate per started course of treatment.

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

- adequate oocytes
- less pain / stress
- lesser cost
- Less complications
- Obtaining adequate number of embryos for implantation

Further progression of technology aimed at minimizing complication rate yet maintaining optimal live birth rates

Louise Brown, was born in 1978 without any fertility drugs



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OHSS-Free Clinic

segmentation of IVF treatment

Does this mean that now we can have as many oocytes and all is safe?

STEP 3

Cryopreserve embryos

-PR higher

-OHSS ZERO

-Ethical issues of CP of embryos

2

GnRH agonist triger

-LPD thus lower PR

-Aggressive luteal support if ET

-Cryo-preserve and subsequent transfer

Antagonist protocol

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

With OHSS free clinic and aneuploidy not being a concern obviously ‘more the better’ appears the best choice

If 'more the better', then freeze all becomes the rule which gives the highest CLBR

Freeze all cycles (3 retrospective cohort studies)

- CLBR was positively correlated with the number of oocytes retrieved and improved as the number of oocytes increased up to 25 in 20687 women undergoing their first IVF cycle using a freeze-all strategy. ***Zhu et al. (2018)***
- CLBR was 55.0%, of one complete freeze-all cycle in 1582 patients for18 months following oocyte retrieval. However, the number of retrieved oocytes was not independently predictive of CLBR. , ***Ozgur et al. (2019)***
- The CLBR increased progressively as the number of oocytes retrieved increased, reaching 97.3% with the retrieval of 43 oocytes in donor cycles. ***Cobo et al. (2015)***

Freeze-all cycles also require a shift in the way the outcome of a cycle is reported Rather than reporting the LBR per started cycle, the CLBR may be a more appropriate outcome measure ***(Maheshwari et al., 2015)***

Two sides of a coin

Minimal or no OHSS

More high quality embryos

High CLBR

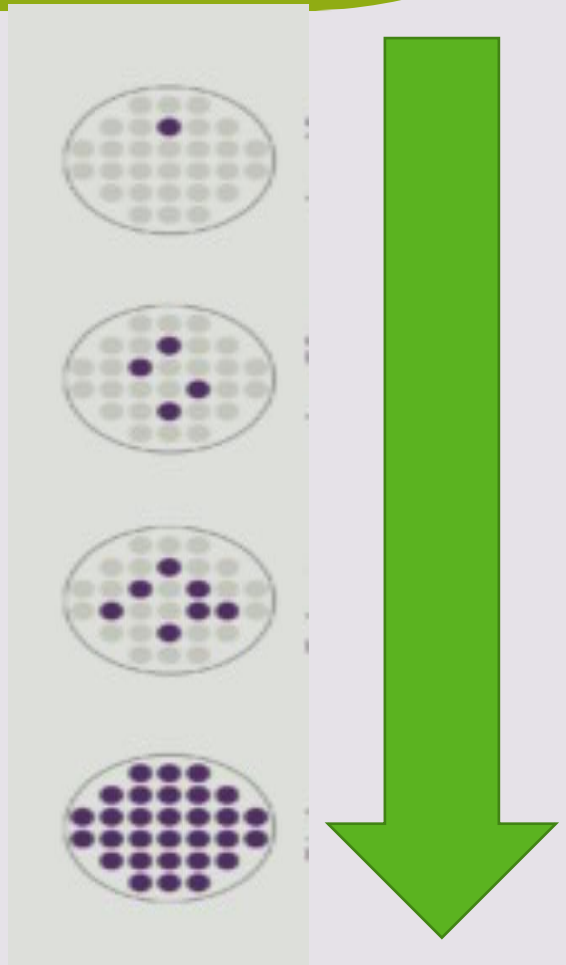
Medical/surgical high stimulation complications

Only frozen ET

Many unused embryos

More is better!

- Low ovarian reserve and older women will have only a definite number of oocytes at all stimulation doses
- Normal reserve women on a conventional stimulation will make 10 to15 oocytes on an average which is also good
- High responder and the young women is our concern when we say ‘**more the better’ or should we aim at ‘adequate is**



Problems of 'more is better' in young high responders

- Possible drawbacks and health risks of a large cohort of follicles to the women undergoing stimulation
- No chance of fresh transfer if too many oocytes are aimed at
- If 'more the better', then freeze all becomes the rule which has its own perils
  - Responsibility and storage of surplus embryos
  - Macrosomia with frozen embryo transfer possibly due to epigenetic with its antecedent health risks
  - Possibility of Increase in childhood cancers

Possible drawbacks and health risks of a large cohort of follicles to the women undergoing stimulation

- Patients are often in considerable pain and discomfort following the retrieval of a large cohort of follicles.
- Extremely high E2 levels are associated with a slight increase in the rare incidence of thromboembolic events (Magnusson et al., 2018).
- Increased risk of bleeding after excessive punctures to remove a large number of oocytes (>30) (Bodri et al., 2008),
- Ovarian enlargement after retrieval may predispose the patients to adnexal torsion.
- Finally, there is a potential for a disaster in case a patient mistakenly receives hCG instead of GnRH agonist for ovulation triggering.

No chance of fresh transfer if too many oocytes are aimed at

Targeted oocyte numbers for fresh embryo transfer with frozen embryos

- When planning for a fresh transfer, a delicate balance exists between ***efficacy and safety*** and OHSS prevention is of utmost importance**.** ***(Steward et al., 2014; Magnusson et al., 2018).***
- In fresh cycles, LBR reaches a plateau or even declines once more than 15–20 oocytes are retrieved. ***(Steward et al 2014; Sunkara et al 2011)***
- Therefore, 10–15 oocytes have become a widely accepted target in IVF cycles targeting fresh as well as frozen transfer.

Yossi Mizrachi, Eran Horowitz, Jacob Farhi, Arieh Raziel and Ariel Weissman. Ovarian stimulation for freeze-all IVF cycles: a systematic review; Human Reproduction Update, pp. 1–18, 2019 doi:10.1093/humupd/dmz037

What is adequate for freeze all cycles?

Even though strong evidence suggests CLBR increases with the number of retrieved oocytes.

- Target no of oocytes should be individualized by age, ovarian reserve & clinical circumstances by individualized COS.
- There are concerns regarding safety and patient's recovery after excessive stimulation.
- Counselling tools for individualization of stimulation goals are being developed to increase efficiency of cycles.
- Best estimate is retrieval of ***15 and 20 oocytes in freeze-all cycles,*** representing good ***balance between safety and efficacy***.

Yossi Mizrachi, Eran Horowitz, Jacob Farhi, Arieh Raziel and Ariel Weissman. Ovarian stimulation for freeze-all IVF cycles: a systematic review; Human Reproduction Update, pp. 1–18, 2019 doi:10.1093/humupd/dmz037

› Hum Reprod. 2018 Jan 1;33(1):58-64. doi: 10.1093/humrep/dex334.

The number of oocytes retrieved during IVF: a balance between efficacy and safety

Åsa Magnusson [1], Karin Källen [2], Ann Thurin-Kjellberg [1], Christina Bergh [1]

Best estimate is retrieval of ***15 and 20 oocytes in freeze-all cycles,*** representing good ***balance between safety and efficacy***.

If ‘more the better’, then freeze all becomes the rule which has its own perils

- Macrosomia with frozen embryo transfer possibly due to epigenetics with its antecedent health risks
- Increase in childhood cancers
- Responsibility and storage of unused surplus embryos after achieving CLBR

Responsibility and storage of unused surplus embryos after achieving CLBR

Journal of Assisted Reproduction and Genetics
https://doi.org/10.1007/s10815-019-01592-w

ASSISTED REPRODUCTION TECHNOLOGIES

Check for updates

Discarding IVF embryos: reporting on global practices

M. Simopoulou[1,2] · K. Sfakianoudis[3] · P. Giannelou[1,3] · A. Rapani[1,2] · E. Maziotis[1,2,4] · P. Tsioulou[1,2] · S. Grigoriadis[1,2] · E. Simopoulos[4] · D. Mantas[5] · M. Lambropoulou[4] · M. Koutsilieris[1] · K. Pantos[3] · J. C. Harper[6]

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The possible destinations of surplus cryopreserved embryos are following:

Donation to other women or couples for reproductive purposes called "embryo adoption".

Donation for investigation after informing couple about the project for embryos use.

Cessation of conservation.

Review > Int J Fertil Womens Med. Jan-Feb 2004;49(1):19-23.

Embryo disposition: the forgotten "child" of in vitro fertilization

Susan C Klock [1]

- **Majority couples ignore their embryos as cannot cope with financial burden of conservation.**

- **Donation of embryos for adoption least preferred option. Only 4% of couples knowingly donate their embryos**

Take home message

'More the better', appears the best option for women with low and normal ovarian reserve but for young, good reserve, high responders including donors, '***keeping a balance between efficacy and safety with careful individualization',*** **appears** of utmost importance.

Best wishes
SGRH IVF team