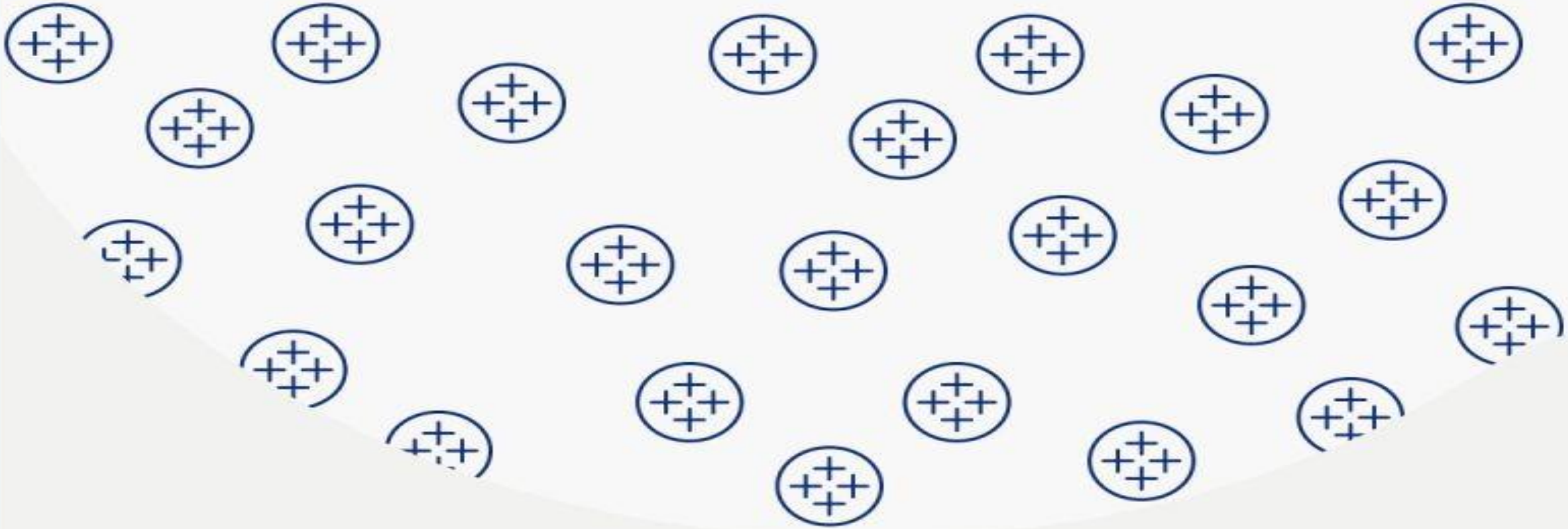

Good practice recommendations on add-ons in reproductive medicine

ESHRE Add-ons working group

2023

eshre

human reproduction

Zanjan University of Medical Sciences

Which add-ons are safe and effective to be used in ART treatment?

ESHRE guideline

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The **innovative nature of ART** combined with the extremely **high motivation of the patients** has opened the door to the wide application of what has become known as **‘add-ons’** in reproductive medicine.

These supplementary options are available to patients in addition to standard fertility procedures, typically incurring **an additional cost**.

Tests
Drugs
Equipment
Complementary or alternative therapies
Laboratory procedures
Surgical interventions

The multidisciplinary working group


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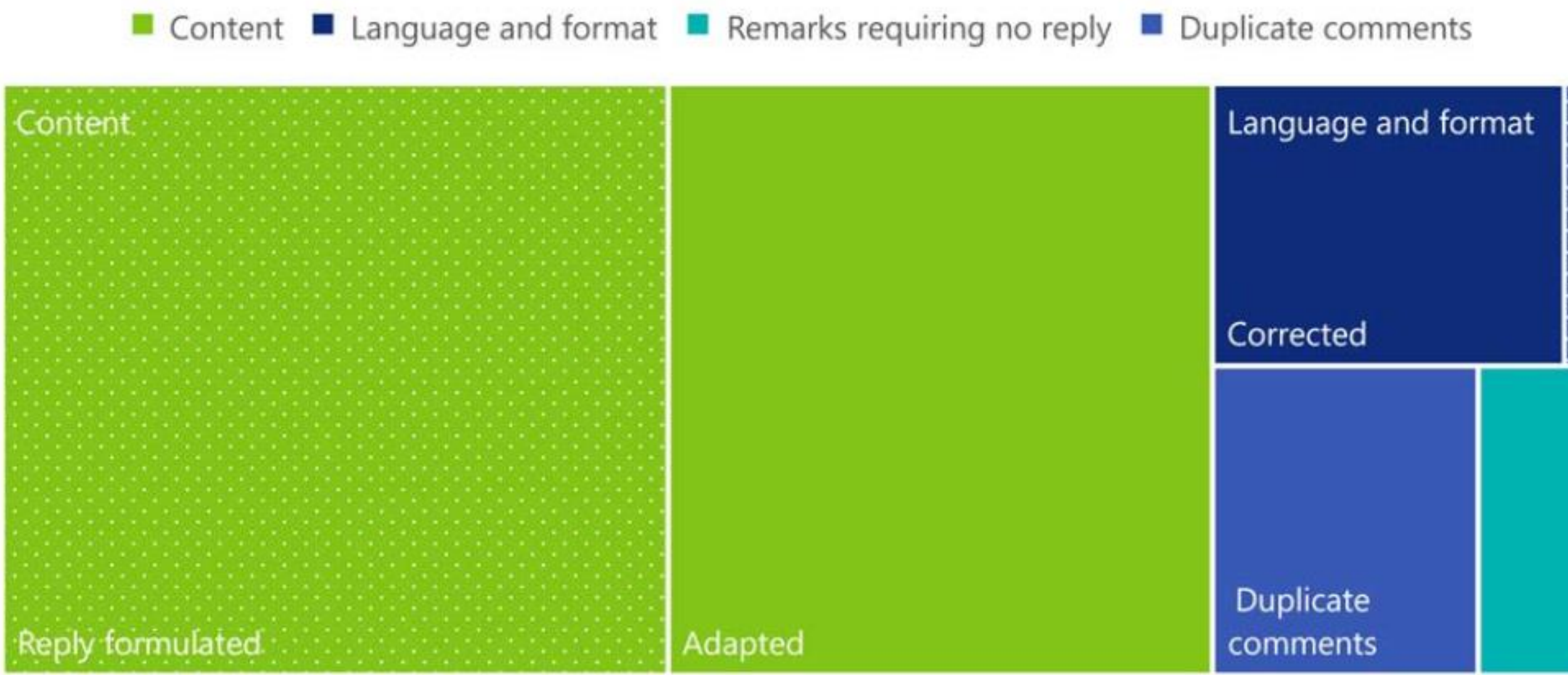
Nathalie Le Clef

Type of comments and actions



OXFORD

human reproduction

Human Reproduction, 2023, **00(0)**, 1–43

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ESHRE Pages

Good practice recommendations on add-ons in reproductive medicine†

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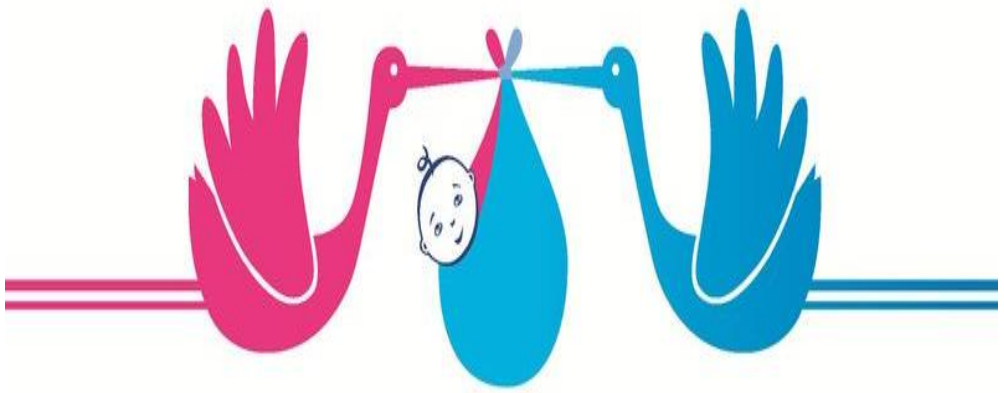
Forty-two recommendations

Diagnosis and diagnostic tests

IVF laboratory tests and interventions

Clinical management



Terminology	Implications
Recommended	The test/intervention can be applied to most patients or to those patient groups for whom it may be of relevance. The recommendation can be adopted as policy in most situations.
Can be considered	Can be applied after a thorough discussion of possible benefits and risks and with close monitoring, follow-up and evaluation.
Currently not recommended for routine clinical use	The test/intervention should not be applied routinely to patients at this stage, but this may change when more evidence on efficacy and safety becomes available. Optionally, the intervention can be applied to a specific patient group.
Not recommended	Based on safety concerns and/or lack of efficacy and/or lack of biological rationale, the test/intervention should not be applied to patients. Further evaluation of these tests/interventions can be done, but only in strict research settings.

1 Screening hysteroscopy

Cochrane review (2 RCT): Hysteroscopy before IVF treatment may increase Live Birth Rate in a mixture of unselected patients.

A recent RCT confirmed a similar LBR when hysteroscopy was performed before IVF treatment or not (Ben Abid et al., **2021**)

Miscarriage Rate: No significant difference in miscarriage rate following screening hysteroscopy compared to no hysteroscopy

A **meta-analysis** focusing on patients with **RIF** reported a significantly higher **LBR** after hysteroscopy compared to patients with RIF who did not have hysteroscopy (Cao et al., 2018).

The results of **three** recent high-quality multi-centre RCTs demonstrated **no significant** improvement in LBR following screening hysteroscopy before IVF treatment.

In **RIF**, hysteroscopy may offer potential benefits, as indicated by the Good Practice Recommendations on RIF **(ESHRE Working Group on Recurrent Implantation Failure, 2023).**

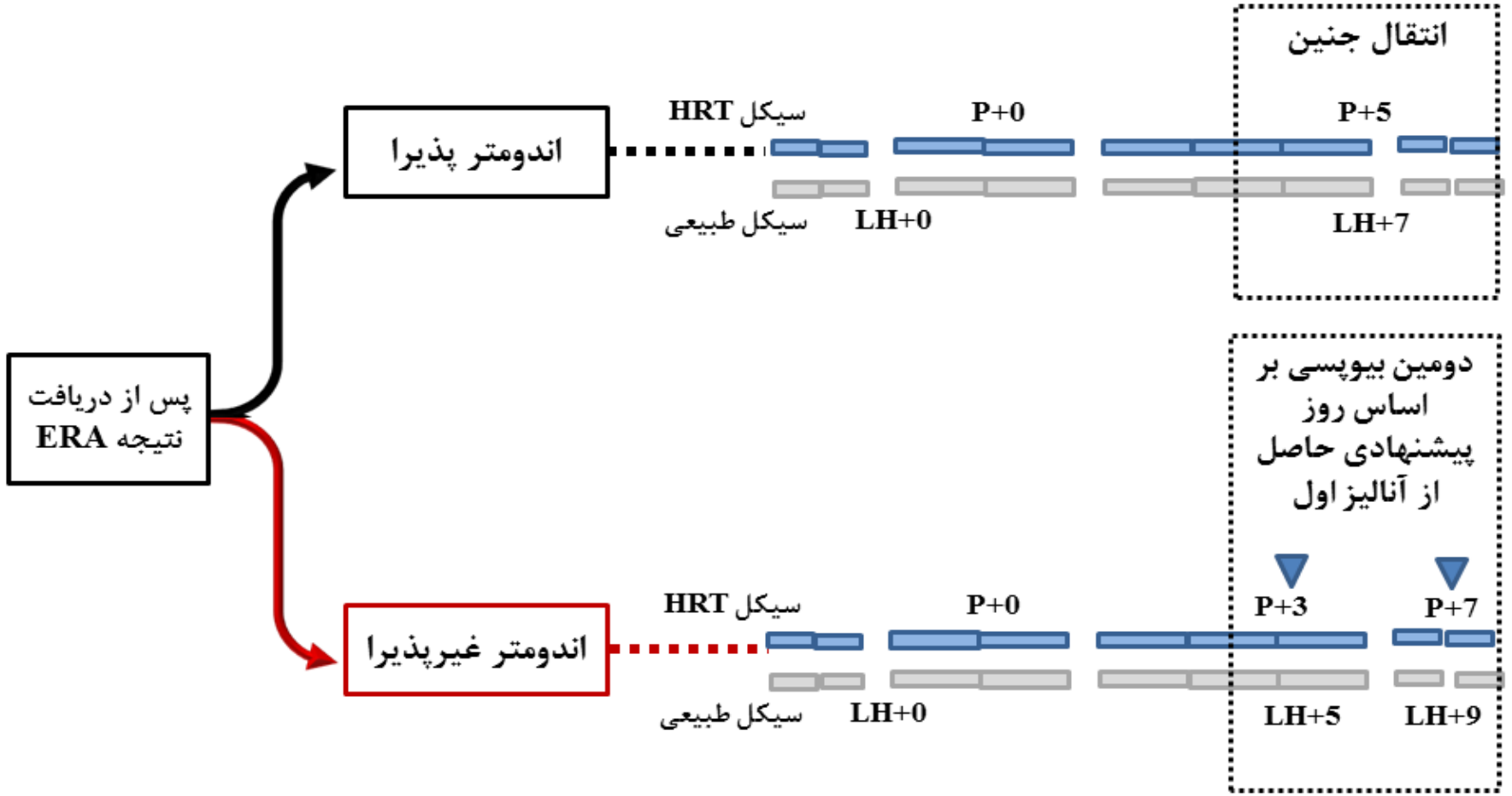
Screening hysteroscopy

Safety: Four trials in the Cochrane review reported complications following hysteroscopy

1. **Screening hysteroscopy is currently not recommended for routine clinical use**

2. **Screening hysteroscopy can be considered in patients with recurrent implantation failure**

3 Endometrial receptivity tests



3 Endometrial receptivity tests

In a study involving 767 women with **cryopreserved euploid blastocysts**, did not significantly improve the LBR compared to standard ET. The LBRs were 58.5% in the intervention group and 61.9% in the control group.
(Doyle et al., 2022)

In a large retrospective multicenter study with 5372 embryo transfers in women with **prior failed transfers**, personalized ET did not result in better outcomes. Both the LBR and cumulative LBR were **significantly lower** after receptivity testing and personalized ET compared to fresh ET. *(Cozzolino et al., 2022)*

3 Endometrial receptivity tests

Safety The endometrial biopsy procedure is considered safe and serious complications are rare

The presently available endometrial receptivity tests are not recommended

4 Reproductive immunology tests

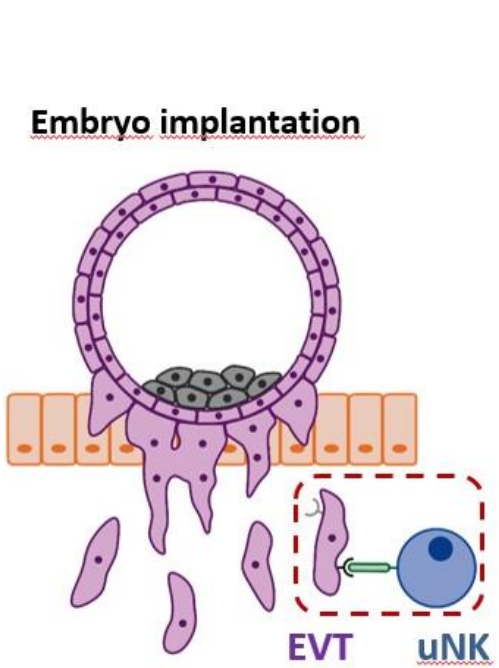
- *This section does not relate to women with auto-immune diseases, including thyroid disease and anti-phospholipid antibody syndrome, or to women who are taking immune treatments, such as steroids, for other medical indications*

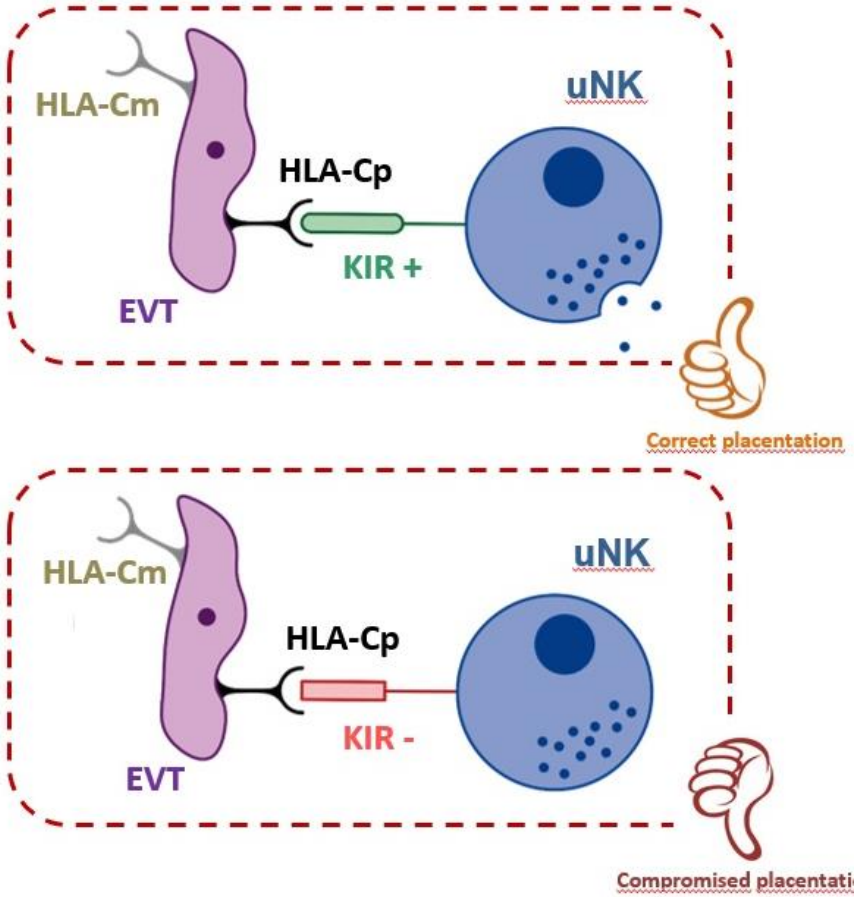
uNK cells

killer-cell immunoglobulin-like receptor (KIR)

HLA genotyping

Tregs, Th1/Th2 ratios, and cytokines such as G-CSF





4 Reproductive immunology tests

1.NK Cell Measurement in Blood: Variability and Cutoff Concerns

Discussion on measuring NK cell levels in blood, highlighting variability and concerns regarding arbitrary cutoffs.

2.Challenges in Interpreting Endometrial Biopsies for NK Cells

Examination of difficulties in interpreting endometrial biopsies for NK cells, including rapid fluctuations and unclear correlations with functions.

3. The benefit on LBR or miscarriage rate is unclear

due to lack of understanding of the mechanisms

Reproductive immunology tests

4 **Peripheral blood tests for immune parameters and uNK-cell testing are not recommended.**

5 **KIR and HLA genotyping is currently not recommended for routine clinical use**

6 Reproductive immunology treatments

Steroids

Lipid emulsion (intralipid) infusion

Intravenous immunoglobulin (IVIG) **(ESHRE guideline on RPL, 2023).**

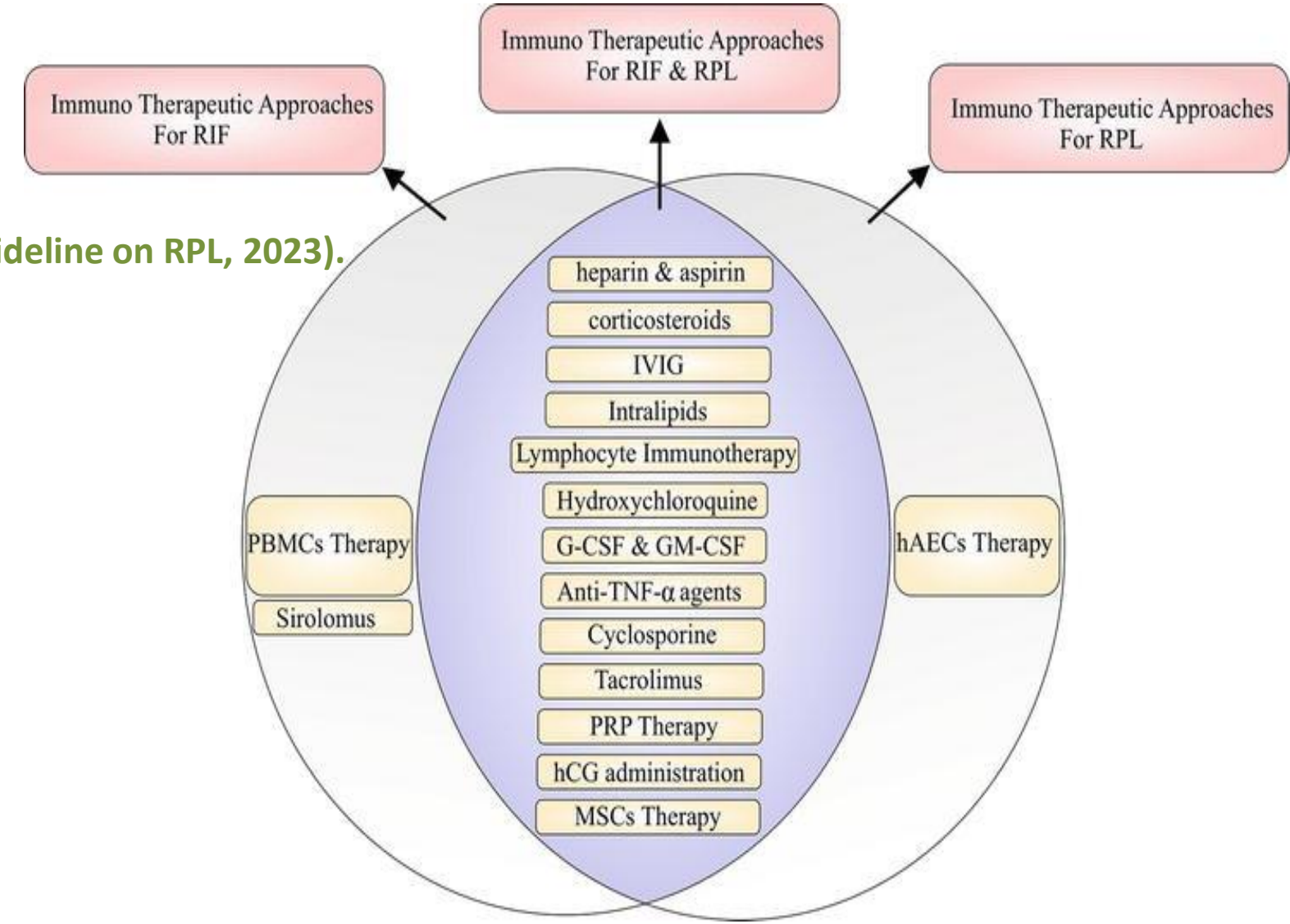
Leucocyte immunization therapy (LIT)

Tacrolimus

Anti-tumour necrosis factor (anti-tnf) agents

G-csf

Hydroxychloroquine



6 Reproductive immunology treatments

Safety

Immunomodulation in ART has many known side effects, some of which are serious.

Those for Intralipid therapy include hepatomegaly, jaundice, cholestasis, splenomegaly, thrombocytopenia, leucopenia, and fat overload syndrome;

IVIG treatment, aseptic meningitis, renal failure, thromboembolism, haemolytic reactions, anaphylactic reactions, lung disease, enteritis, dermatologic disorders, and infectious diseases have been reported;

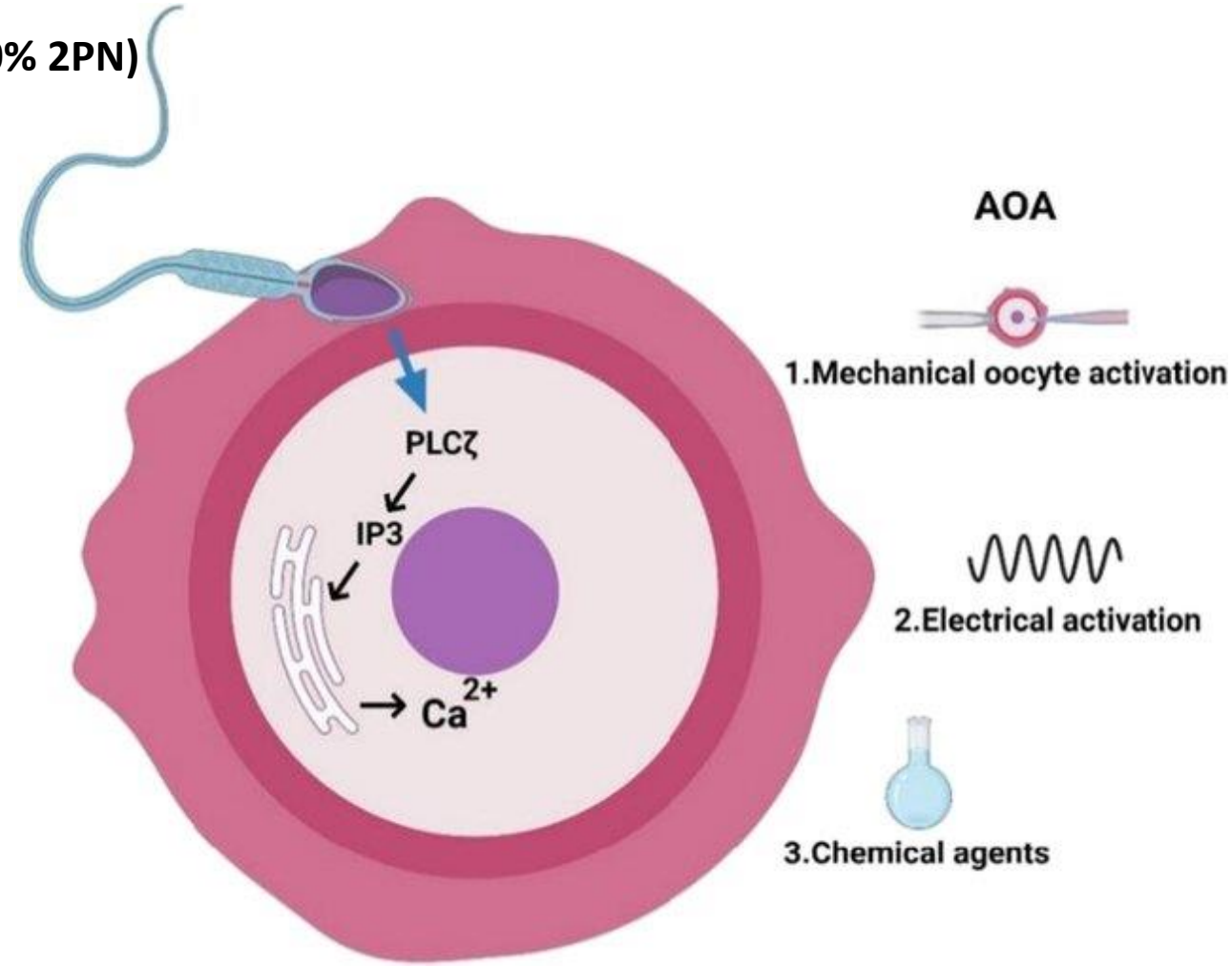
Immunomodulating treatments, such as Intralipid, IVIG, rh-LIF, PBMCs, and anti-TNF, are not recommended.

7 Artificial oocyte activation

Complete fertilization failure in a previous IVF/ICSI cycle (0% 2PN)

Poor fertilization outcome (<30%)

Cases of severe male factor infertility

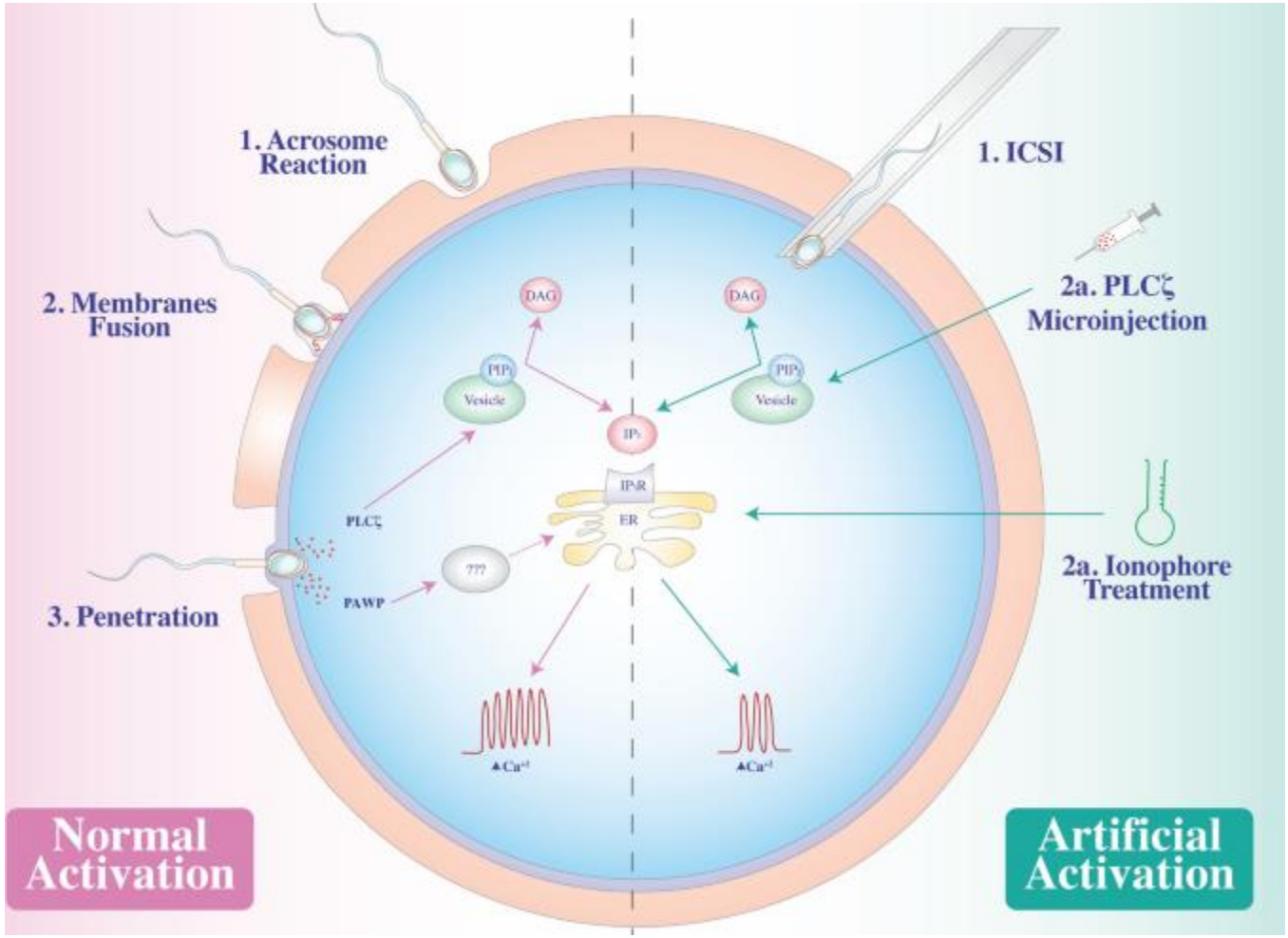


Artificial oocyte activation

Efficacy

A meta-analysis pooling results of 14 studies (4 RCTs, 4 prospective, 5 retrospective and one historical cohort study) showed that AOA with any kind of calcium ionophore increased **LBR** specifically in patients with **previous fertilization failure or low fertilization rate, embryo developmental problems**

Artificial oocyte activation



Artificial oocyte activation

- **Safety**

Ca^{2+}-ionophores can bind Ca^{2+}-cations and owing to their hydrophobic properties they form a complex at the lipid bilayer of the membrane.

- Ionophores themselves do not necessarily enter the oocyte

- no increase in birth defects

Continuous monitoring and assessment of the long-term effects and safety of children

Artificial oocyte activation

7 Artificial oocyte activation is currently not recommended for routine clinical use

8 Artificial oocyte activation is recommended for complete activation failure (0% 2PN)

very low fertilization (<30% fertilization)

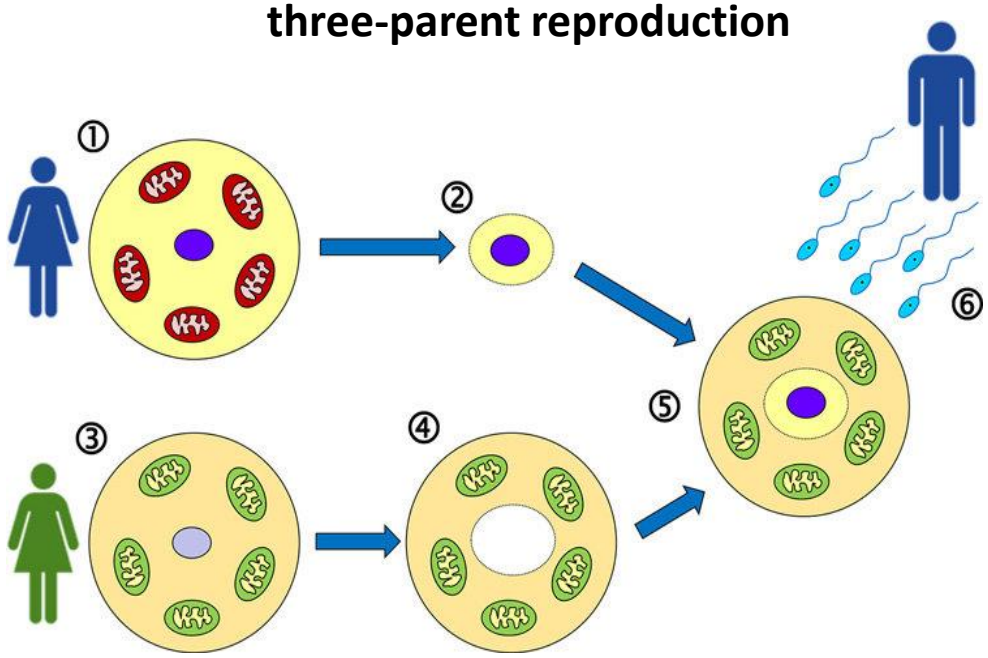
Globozoospermia

Proper indication

9 Mitochondrial replacement therapy

- ✓ Avoid the transmission of mitochondrial DNA (mtDNA) diseases through the mtDNA present in the oocyte
- ➢ Improve the quality of the oocytes (add-on) in women with difficulties in conceiving linked to oocyte quality and/or fertilization failure

three-parent reproduction



Efficacy & Safety
limited clinical data

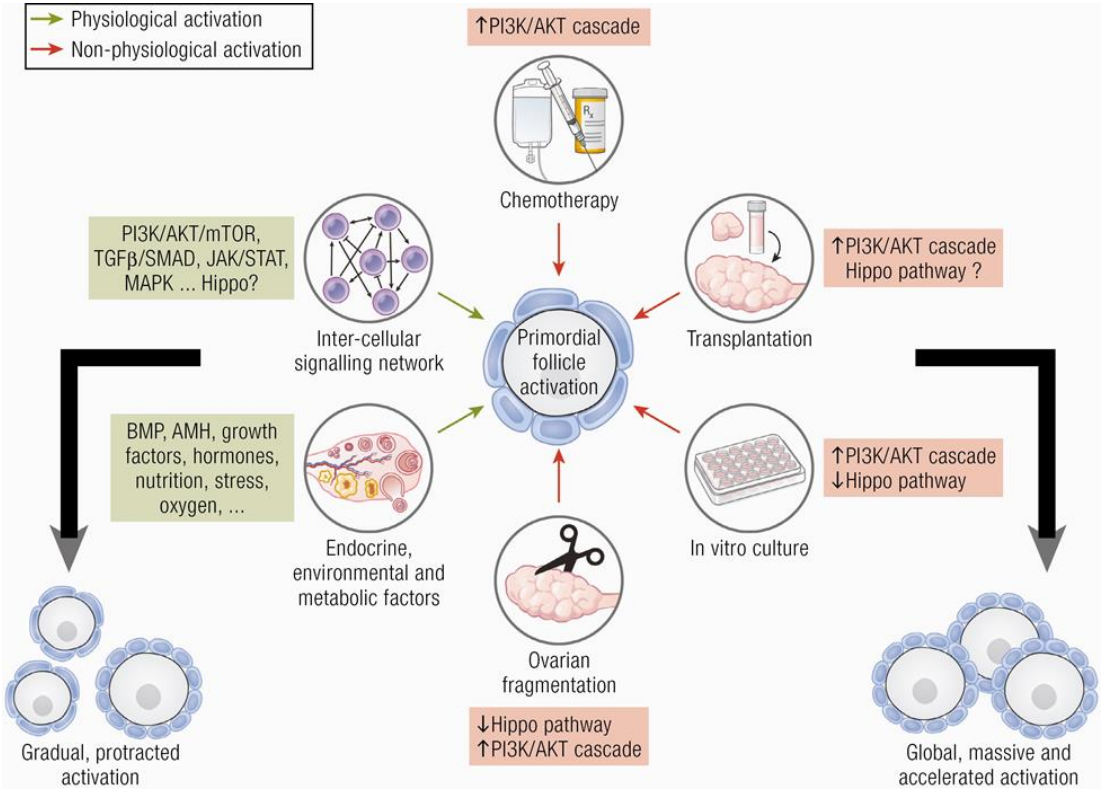
Mitochondrial replacement therapy to affect oocyte quality is not recommended

10 In vitro activation of dormant follicles

Premature ovarian insufficiency (POI)

Recommendation

Considering the limited efficacy, potential high cost, and safety concerns, IVA of dormant follicles **is considered experimental** and can only be applied within **strict research protocols**



11 IVM, Clinical IVM

IVM is applied to obtain mature oocytes from immature cumulus–oocyte complexes retrieved from antral follicles

- ✓ PCOS
- ✓ Before the start of gonadotoxic treatment (ESHRE Guideline Group on Female Fertility Preservation et al., 2020)

Clinical IVM: a natural cycle with minimal or no ovarian stimulation, and OPU is performed when the leading follicle measures between 9 and 12 mm

Safety

Do not indicate an increase in imprinting errors after IVM, or a difference in the neonatal health and developmental outcome of children

- ➢ **limited data and need further exploration**

Rescue IVM or natural cycle IVF/M

Rescue IVM: IVM of the immature oocytes (prophase I (PI) or metaphase I (MI))

- ✓ In poor responders
- ✓ poor prognosis patients

Safety

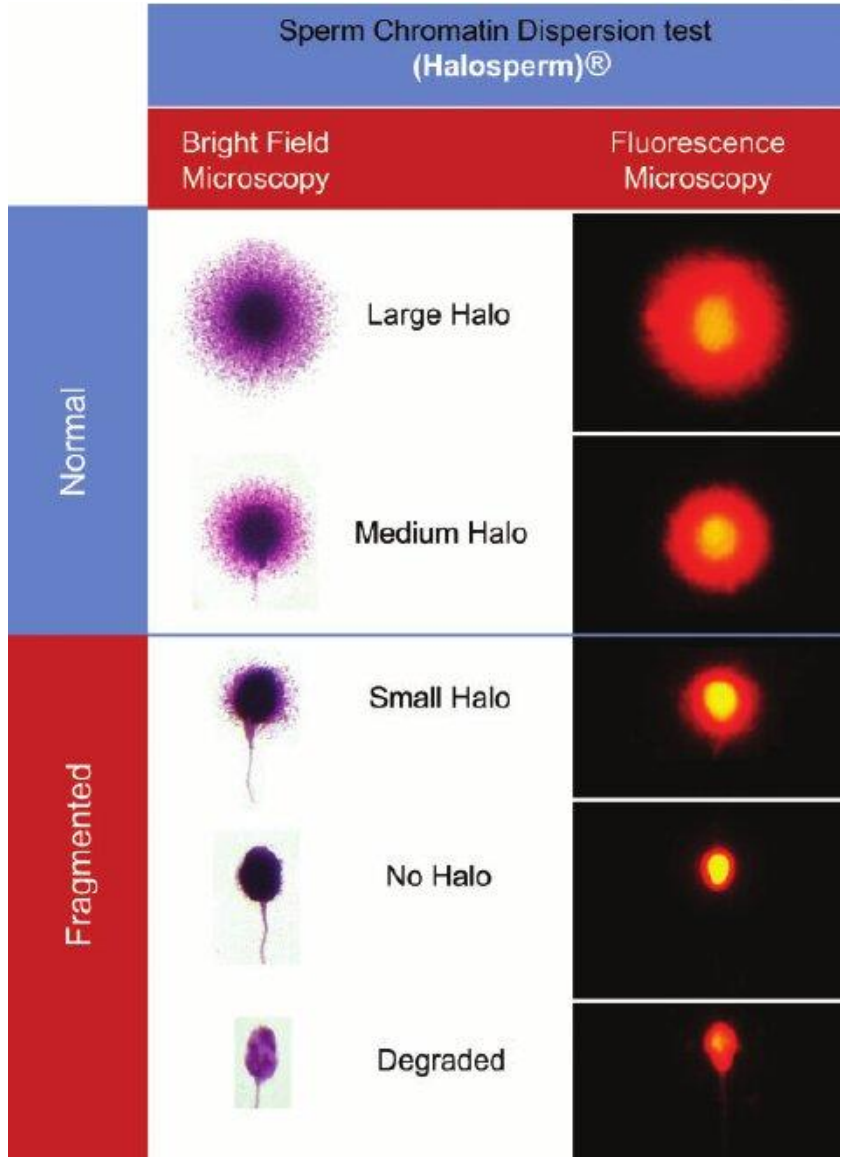
The safety of rescue IVM is questionable since these oocytes commonly have meiotic defects and are of poor quality

- ➢ **There is a lack of established effectiveness, procedural reliability and long-term safety data for both clinical and rescue IVM in infertile patient**

12 Sperm DNA damage testing

- **TUNEL**
- **In Situ Nick Translation Assay (ISNT)**
- **Sperm Chromatin Structure Assay (SCSA)**
- **Sperm Chromatin Dispersion Test (SCD)**
- **Comet Assay**

- Varicocele, accessory gland infection, advanced paternal age, cancer, exposure to environmental toxins, and lifestyle factors



Sperm DNA damage testing

Efficacy

- Systematic review and meta-analysis: infertile men had higher SDF compared to fertile counterparts
- weak evidence for the predictive value of SDF testing in patients with **varicocele** and **RPL** suggesting that SDF testing may have **a limited value in these patients**
- In an RCT, 302 men with abnormal SDF were randomized to density gradient centrifugation, physiological ICSI (PICSI) or MACS. Applying advanced sperm selection techniques (PICSI or MACS), rather than DGC, resulted in higher CPRs.
- In contrast, in a prospective cohort study, including 80 males with DFI 30%, no difference in CPR was found with the use of **MACS** (Mei et al., 2022).
- TESE: meta-analysis: higher CPR with testicular sperm with high SDF than with ejaculated sperm

- lack of matching for confounding factors (e.g. lifestyle factors, empiric treatments)

12 Sperm DNA damage testing

Safety

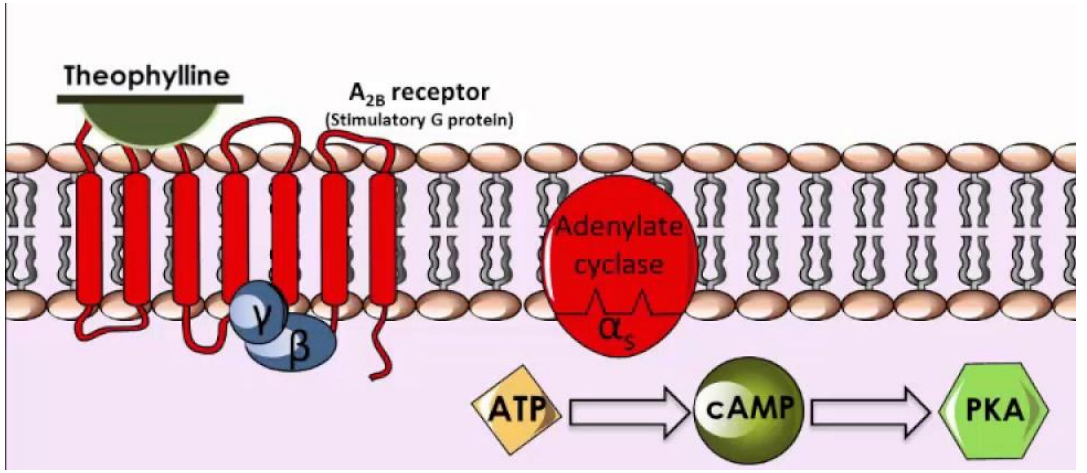
No safety issues have been reported

There is **insufficient evidence** for the relevance of SDF tests to predict pregnancy or guide treatment decisions. Further research in this field is strongly recommended to enhance our understanding and knowledge.

Artificial sperm activation

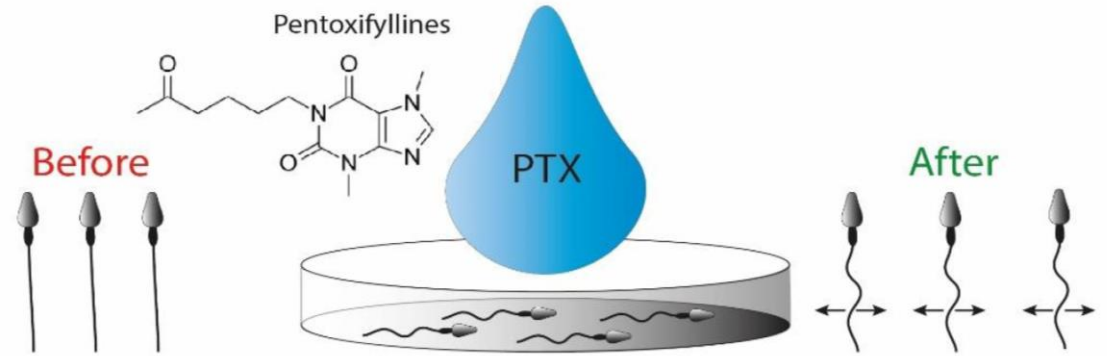
using phosphodiesterase (PDE) inhibitors to increase cAMP levels.

- **Pentoxifylline (PTX)**
- **Theophylline**



Any effect on sperm motility is expected within 3– 5 min and lasts for 1–2 h.

At the same concentration, PTX and theophylline have comparable activity, however, the halflife of theophylline is 10-fold higher



Artificial sperm activation

Efficacy
An RCT on 120 patients with mild to moderate asthenozoospermia revealed that use of spermatozoa artificially stimulated with **PTX** resulted in a significantly higher CPR**.**

In a sibling oocyte approach, ICSI with frozen-thawed sperm, activated with ready-to-use **theophylline**, resulted in significantly higher rates of fertilization, blastocyst formation, clinical pregnancy, and LBR.

Kartagener syndrome and related structural problems, any treatment with PDE inhibitors will **be ineffective**

Safety
Carryover of PTX and theophylline to oocytes during ICSI and contact with embryos should be kept to a minimum.

Artificial sperm activation

Recommendation

There are no studies evaluating artificial sperm activation treatment in a general male infertility population.

- It is crucial to conduct continuous monitoring and follow-up to assess the **long-term effects** and safety of children born through this approach.

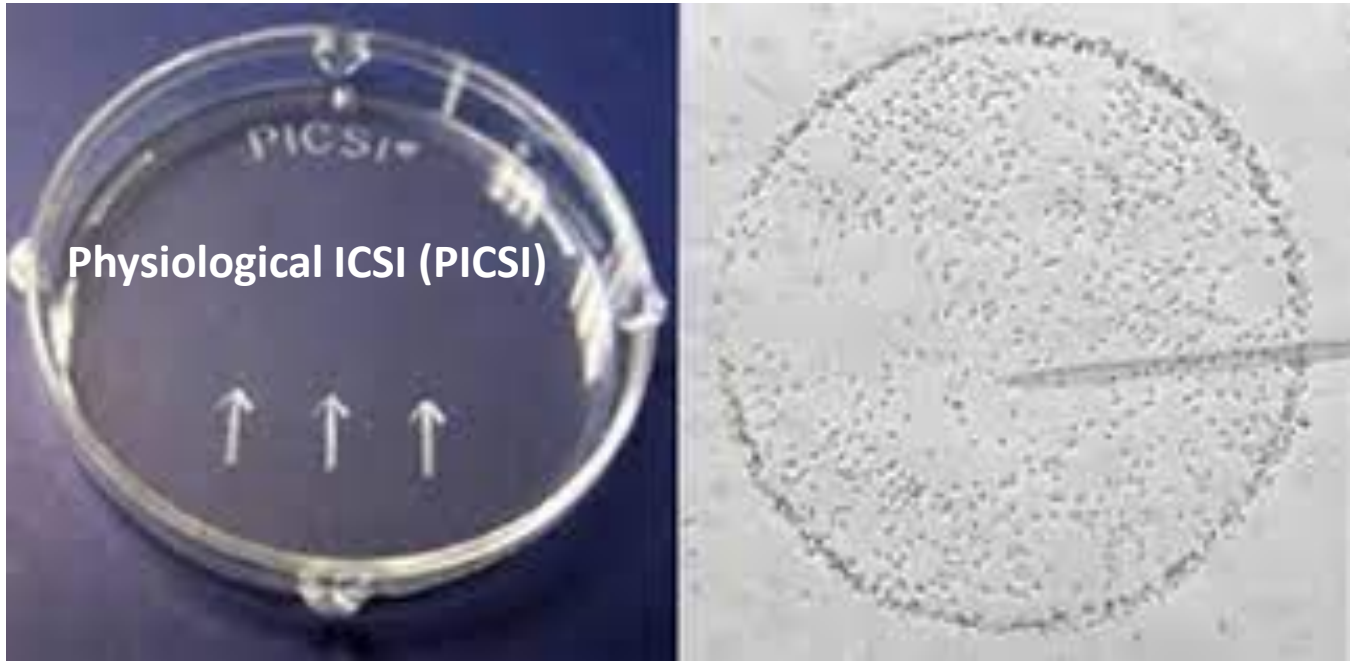
13 Artificial sperm activation is currently not recommended for routine clinical use.

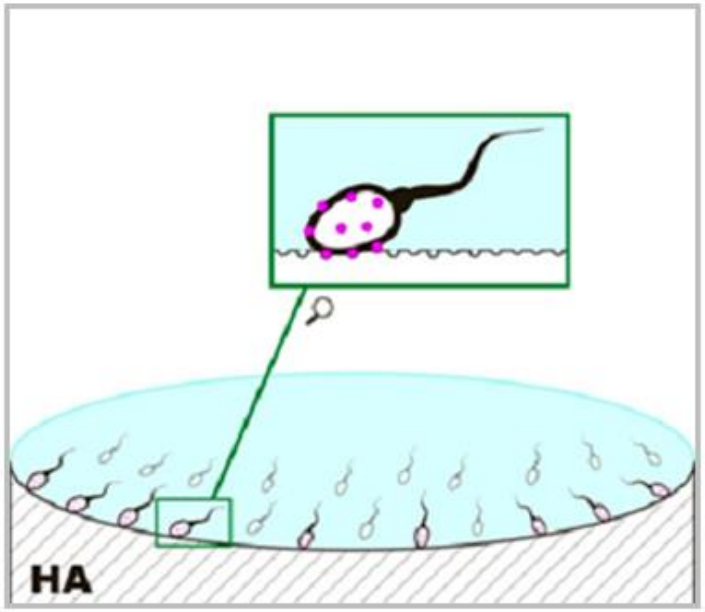
14 Artificial sperm activation is recommended for patients with **primary or secondary total asthenozoospermia** which are not the result of axonemal structure defects.

15 Advanced methods of sperm evaluation and selection

- **Sperm hyaluronic binding assay**

The HA assay is based on the mature and intact sperm surface containing a receptor for HA or hyaluronidase, which binds to HA coated on the surface





The principle of the PICSI method is that binding to HA mimics the natural mechanism of sperm selection, assuming that sperm expressing the HA receptor would be of high quality.

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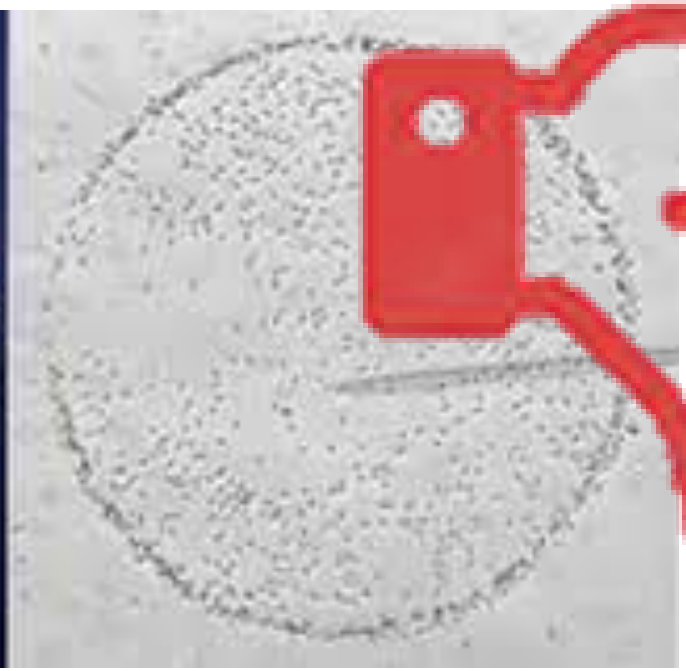
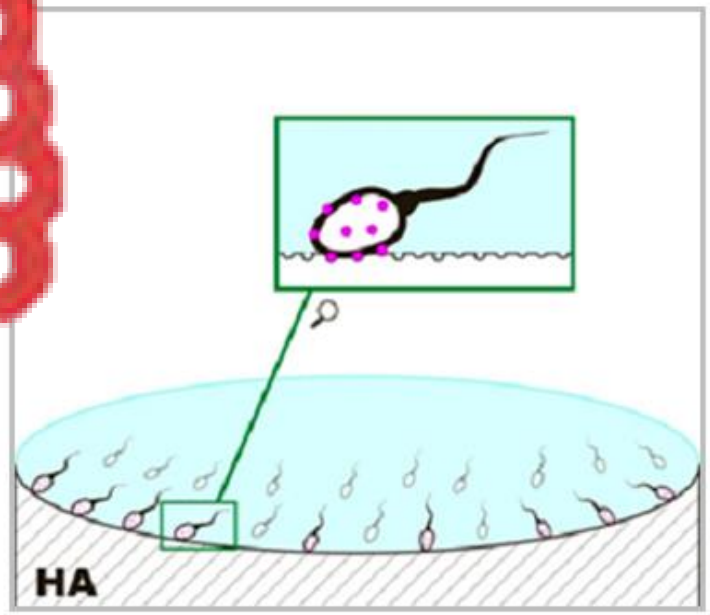




The principle of the PICSI method is that binding to HA mimics the natural mechanism of sperm selection, assuming that sperm expressing the HA receptor would be of high quality.

- **Efficacy**

Cochrane systematic review and meta-analysis suggest that PICSI or sperm selection using HBA may have little or no effect on LBR but may reduce miscarriage

- **Safety**

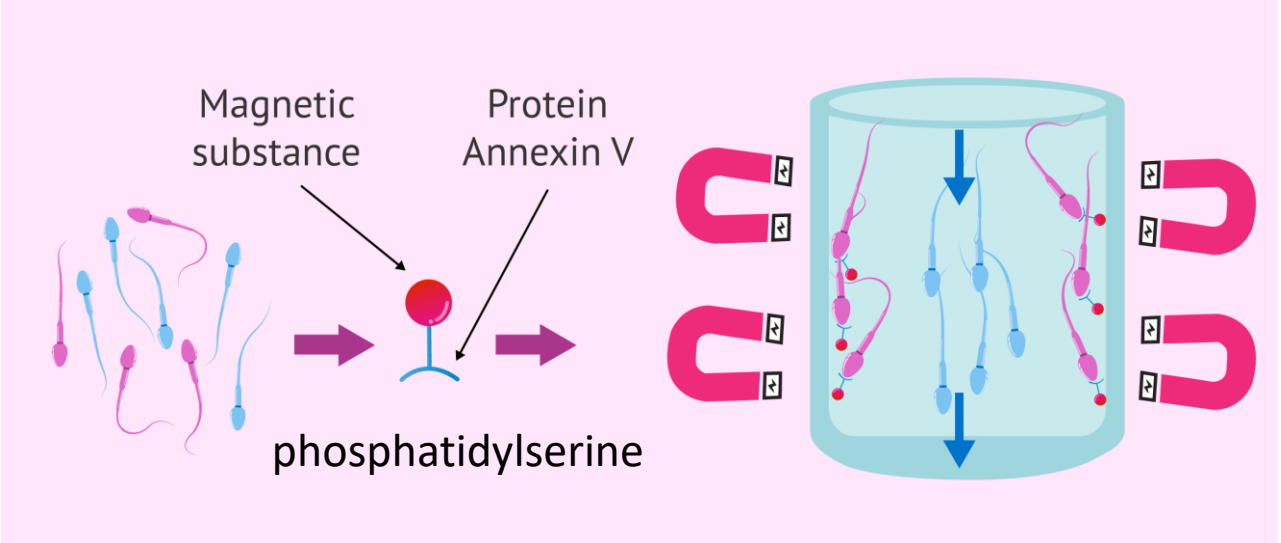
No safety issues have been shown. However, the manufacturer's recommendation that the optimal temperature for sperm HBA binding is **30 ◦C** should be taken into consideration when performing ICSI using the PICSI dish.

- **Recommendation**

The sperm hyaluronic binding assay has limited clinical value about the prediction of fertilization or pregnancy, or guiding of treatment selection, which is further hampered by limitations in the standardization of the test.
The method may offer an advantage in **some categories of patients**.
Similarly, PICSI, as a sperm selection method, may have little or **no effect on live birth or CPR**

16 Magnetic-activated cell sorting

The semen sample is passed through a column containing annexin V microbeads and apoptotic sperm expressing externalized phosphatidylserine are retained within the column and are thus deselected. The remaining selected sperm were shown to have better nuclear DNA integrity



- **Efficacy**

Cochrane systematic review and meta-analysis reported insufficient evidence of an effect of MACS sperm selection on **LBR** or **miscarriage.**

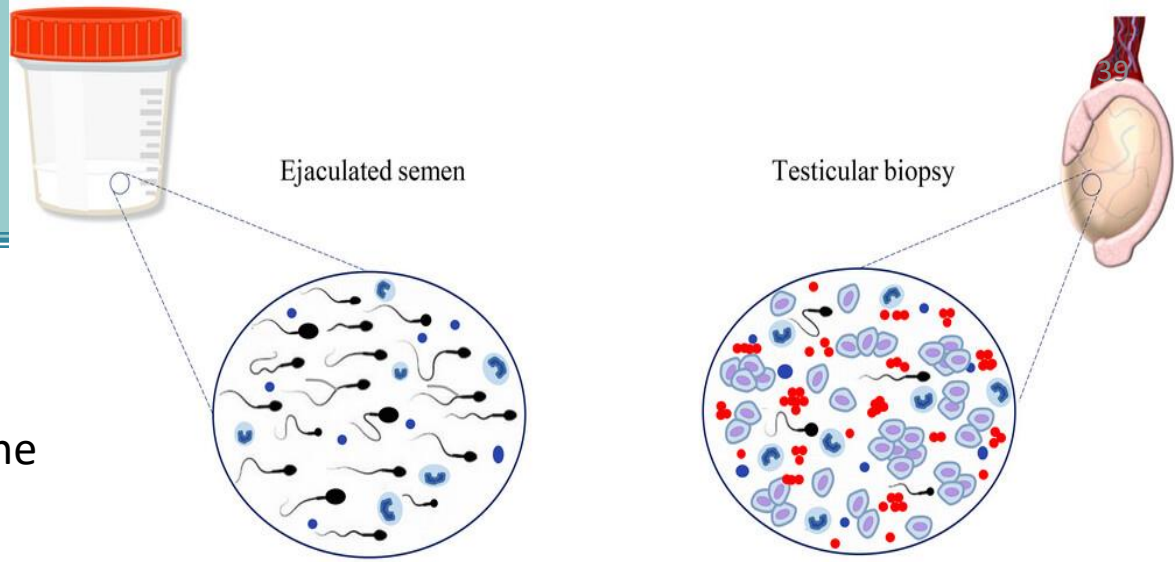
MACS is currently not recommended for routine clinical use.

- **Safety**

There are **no data available** regarding the safety of using MACS

17 Microfluidics

Microfluidics-based technologies have been adapted for sperm selection and preparation, without the need for centrifugation, aiming to mimic the geometry of micro-confined regions within the female reproductive tract

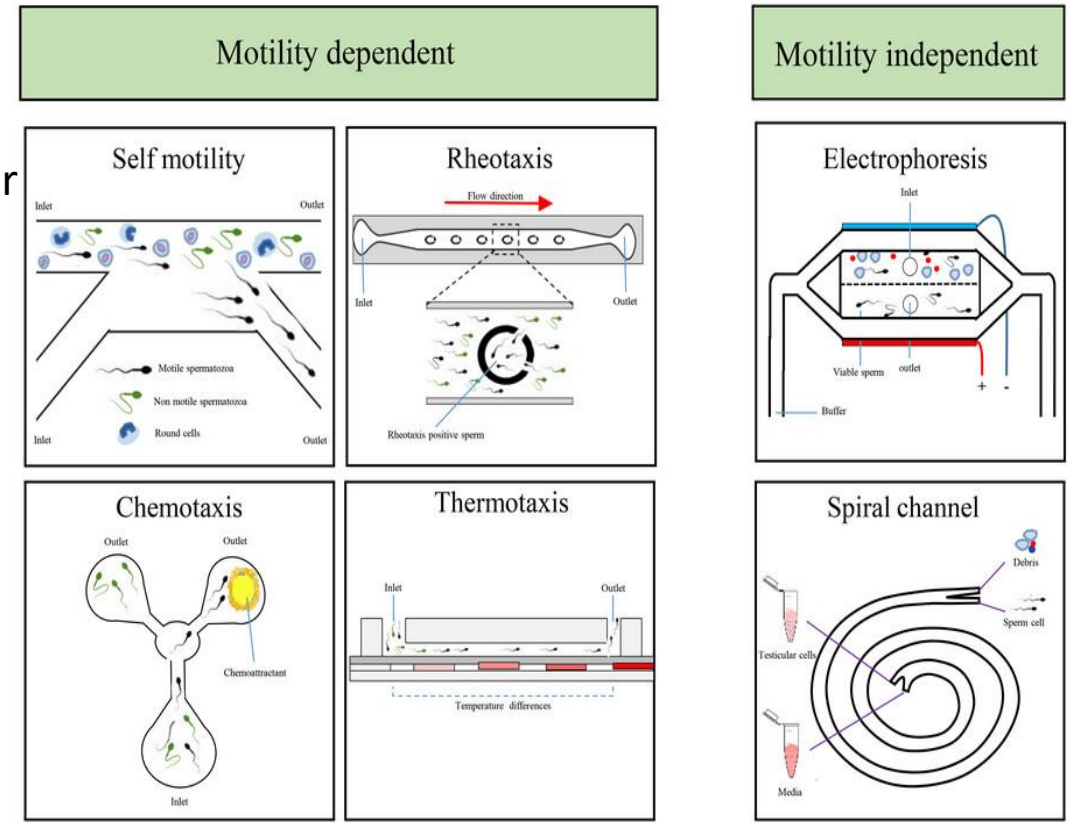


- ✓ Only one RCT reporting benefit on LBR No harms reported,
- ✓ Observational study showed no benefit of using microfluidics for sperm selection.

Recommendation

Further research is required to validate these findings and provide a more robust evidence base before making widespread recommendations.

➢ **can be considered**



18 Intracytoplasmic morphologic sperm injection (IMSI)

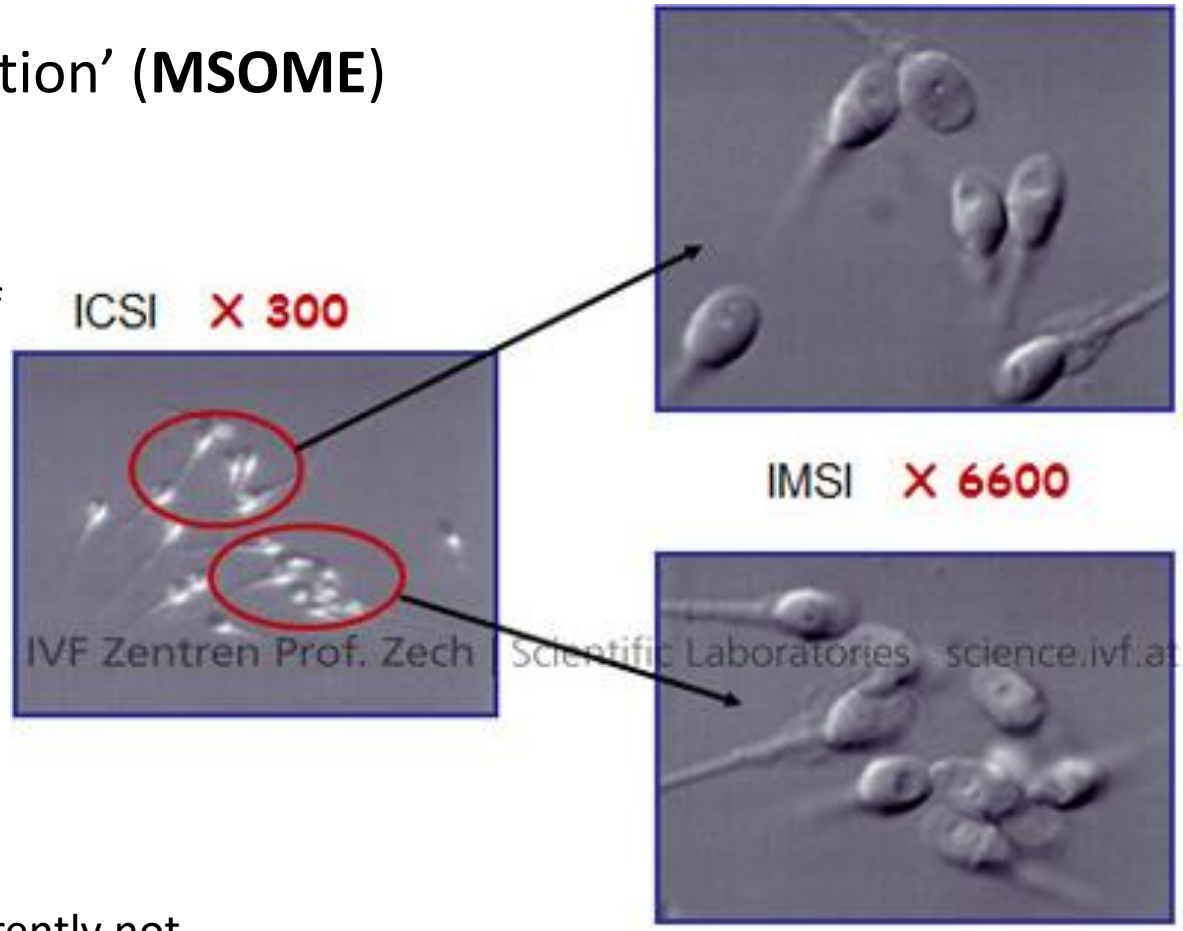
‘motile sperm organelle morphology examination’ (**MSOME**)

- **Efficacy**

A Cochrane systematic review and meta-analysis: No evidence of benefit on **LBR** or **miscarriage rate**

- **Safety**

no data available



Intracytoplasmic morphologic sperm injection is currently not recommended for routine clinical use

Growth factor-supplemented embryo culture medium

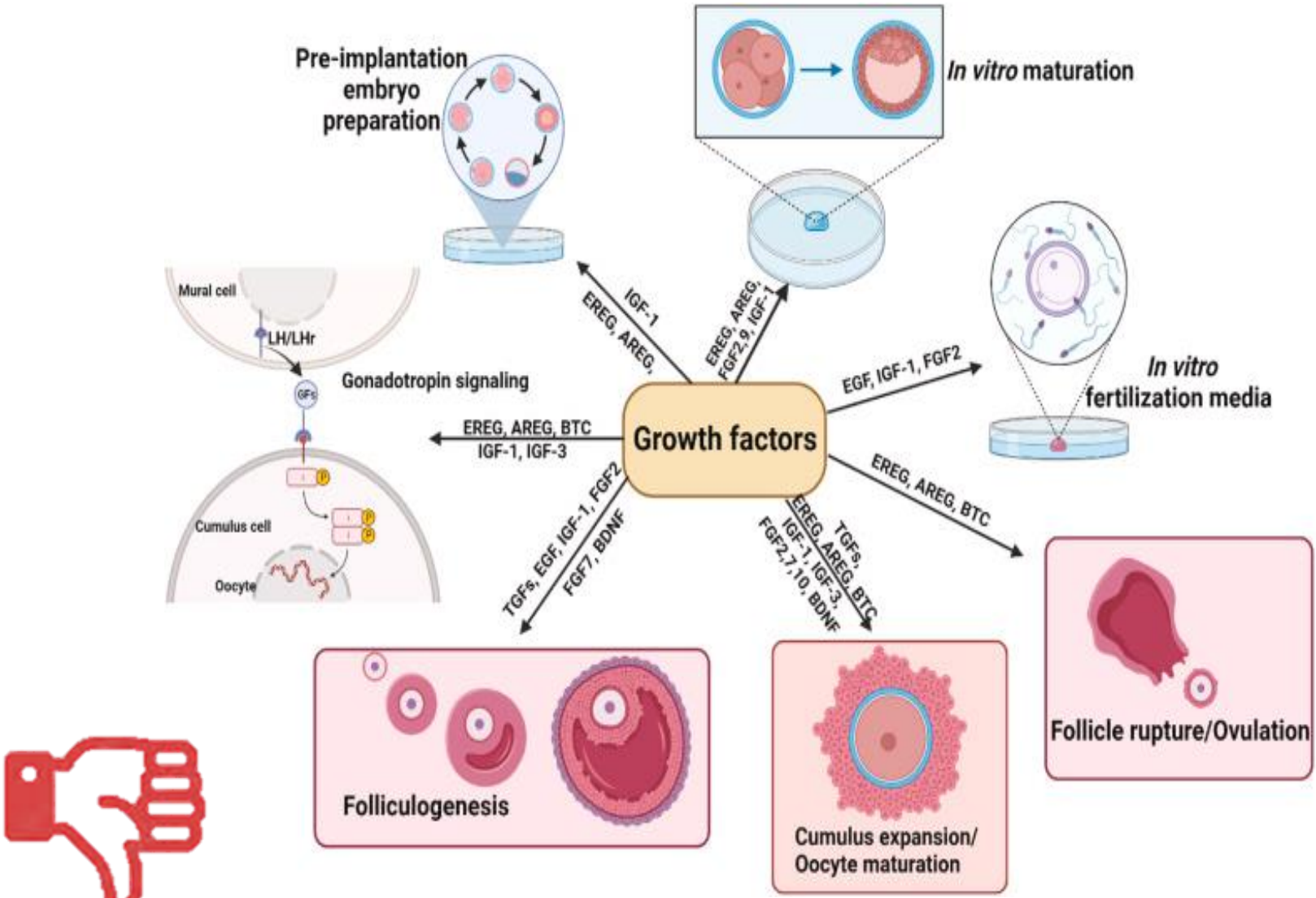
➢ **Efficacy**

A Cochrane systematic review and meta-analysis:
No evidence of benefit on **LBR** or **miscarriage rate**

➢ **Safety**

Theoretical harms, but not reported

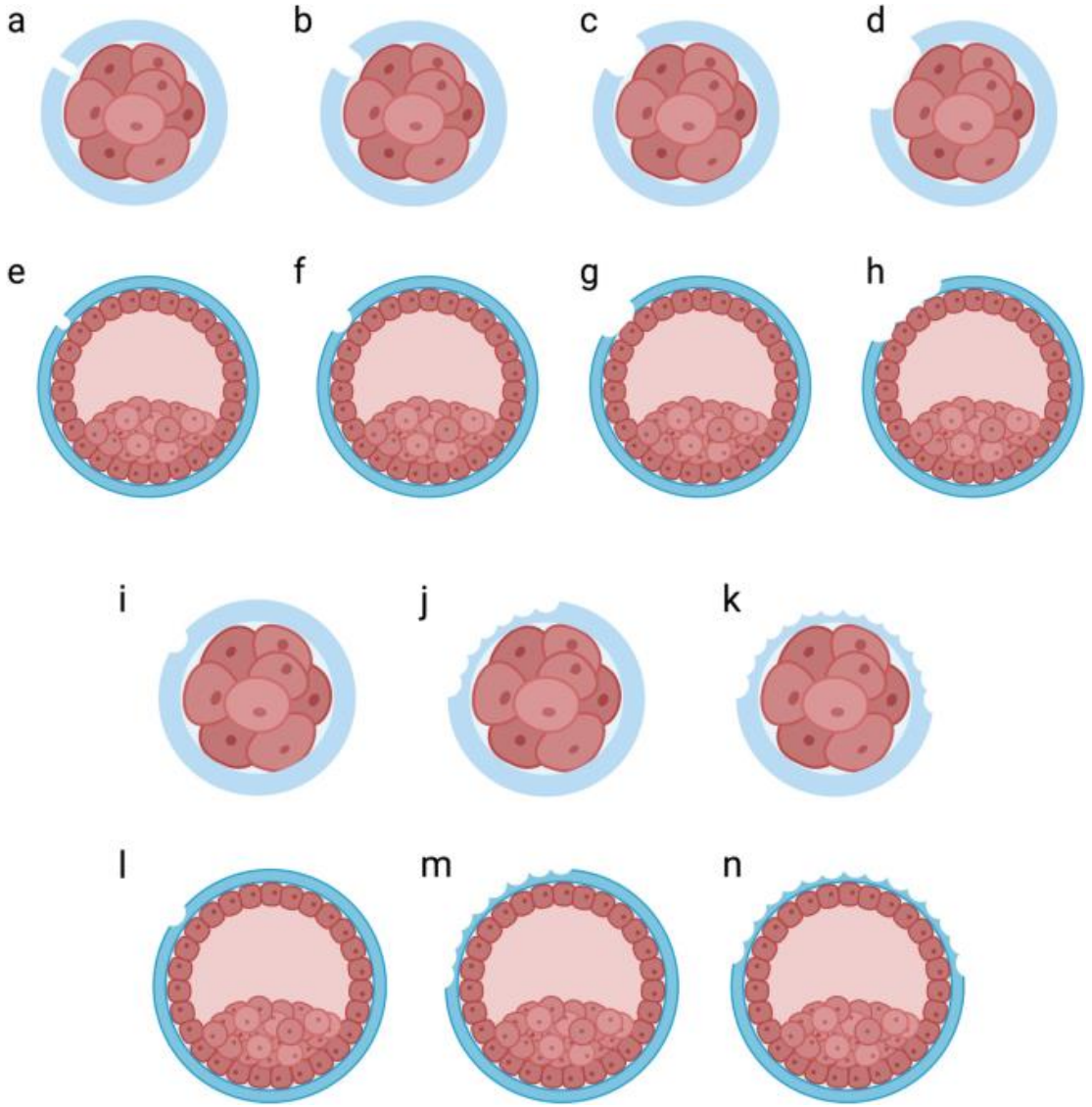
As growth factors act in **both positive** and **negative synergy** to produce an effect, the addition of a single growth factor to embryo culture media **is questionable** and will not necessarily elicit a beneficial effect. It is suggested that, if not well regulated, exogenous growth factors could have adverse effects on embryo development



Assisted hatching

mechanically, chemically or using a laser

thinning
creating a small hole
a large hole
complete removal of the ZP



- **Efficacy**

A Cochrane systematic review and meta-analysis:
No evidence of benefit on LBR or miscarriage rate

- **Safety**

increased multiple pregnancy rate (monozygotic twinning)

Pre-implantation genetic testing for aneuploidy

RCT	Patients	Controls	Embryo biopsy	Genetic platform	LBR (unless otherwise indicated)	Miscarriage rate
Yang *et al.* (2012b)	55 good-prognosis patients, 1st IVF cycle Age: 31.2 ± 2.5	48 controls Age: 31.5 ± 2.7	Blastocyst	aCGH	Higher[1] 38/55 (69.1%) vs 20/48 (41.7%) ($P = 0.009$) (per ET)	No difference 1/55 (2.6%) vs 2/48 (9.1%) ($P = 0.597$)
Forman *et al.* (2013)	89 single euploid blastocyst transfer, normal ovarian reserve, ≤1 previous IVF failure Age: 35.1 ± 3.9	86 double blastocyst transfer Age: 34.5 ± 4.7	Blastocyst	qPCR	No difference[2] 60.7% vs 65.1% (RR 0.9; 95% CI 0.7 to 1.2) (per ET)	Not reported
Scott *et al.* (2013)	134 blastocysts/ 72 patients with normal ovarian reserve, ≤1 previous IVF failure Age: 32.2 ± 0.5	163 blastocysts/ 83 patients Age: 32.4 ± 0.5	Blastocyst	qPCR	Higher 61/72 (84.7%) vs 56/83 (67.5%) (RR 1.26; 95% CI 1.06 to 1.53; $P = 0.01$) (per ET)	No difference 7/61 (11.5%) vs 14/70 (20.0%); $P = 0.2$)
Rubio *et al.* (2017)	538 Day 3 embryos from 138 patients Age: 38–41	581 Day 3 embryos/ 140 patients Age: 38–41	Day 3	aCGH	No difference 44/138 (31.9%) vs 26/140 (18.6%) (OR 2.381, 95% CI 1.343 to 4.223)	Lower 1/37 (2.7%) vs 16/41 (39.0%) (OR 0.06, 95% CI 0.008 to 0.48)
Verpoest *et al.* (2018)	205 patients (177 transfers) Age: 38.6 ± 1.4	191 patients (249 transfers) Age: 38.6 ± 1.4	Polar body	aCGH	No difference 50/205 (24%) vs 45/ 191(24%) (RR 1.06; 95% CI 0.75 to 1.50; $P = 0.75$) (per patient)	Lower 14/205 (7%) vs 27/ 191 (14%) (RR 0.48; 95% CI 0.26 to 0.90; $P = 0.02$)
Munné *et al.* (2019)	330 patients undergoing IVF with at least two blastocysts that could be biopsied Age: 33.7 ± 3.59	331 patients undergoing IVF with at least two blastocysts that could be biopsied Age: 33.8 ± 3.58	Blastocyst	NGS	No difference[3] 137/274 (50%) vs 143/313 (46%) (per ET) per ITT (per patient): 138/ 330 (41.8%) vs 144/ 331 (43.5%)	No difference 27/274 (9.9%) vs 30/ 313 (9.6%)
Yan *et al.* (2021)	606 women with three or more good-quality blastocysts Age: 29.1 ± 3.6	606 women with three or more good-quality blastocysts Age: 29.2 ± 3.5	Blastocyst	NGS	Lower (per patient) 458/606 (77.2%) vs 496/606 (81.8%) (absolute difference, −4.6 percentage points; 95% CI −9.2 to −0.0; $P < 0.001$)	Lower 8.7% and 12.6%, (RR 0.69; 95% CI 0.49 to 0.98)

21 Pre-implantation genetic testing for aneuploidy

meta-analysis, including 15 studies: An increased risk of certain adverse obstetric and neonatal outcomes was reported, namely **low birthweight, preterm delivery, hypertensive disorders of pregnancy, and lower gestational age and birthweight** in PGT pregnancies relative to spontaneously conceived pregnancies.

In the comparison of **PGT pregnancies to IVF/ICSI** pregnancies, the reviewers reported a **decreased risk of very preterm delivery** and **very low birthweight** in PGT pregnancies, and an **increased risk of hypertensive disorders** of pregnancy

Harms include disposal of viable embryos and IUGR

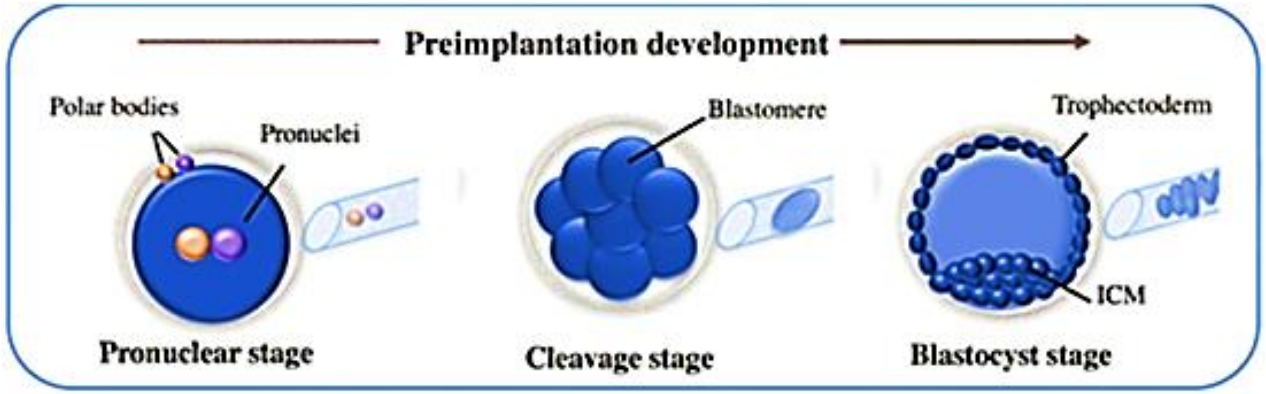
The current available data for PGT-A using current methodology for genetic analysis indicate **limited improvement in LBR**.

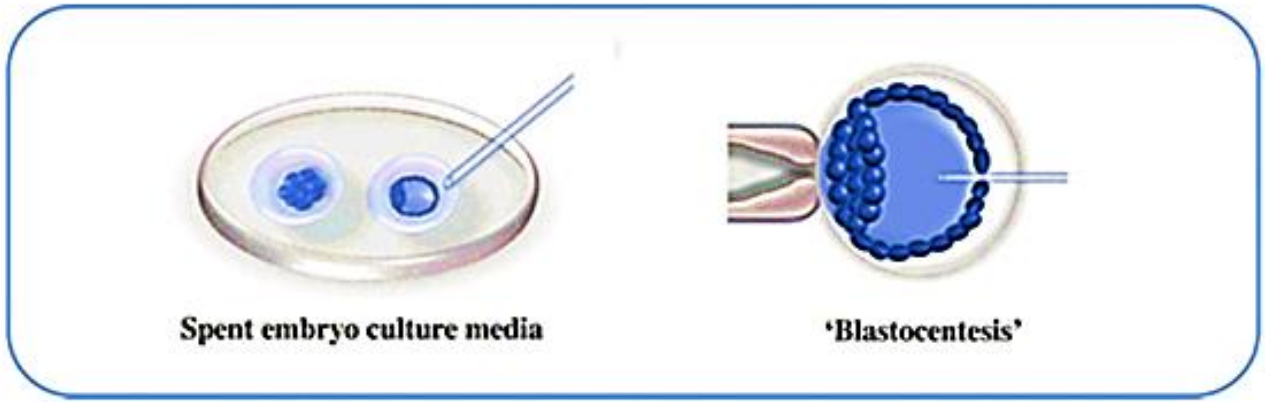
- **Pre-implantation genetic testing for aneuploidy is currently not recommended for routine clinical use.**

22 Non-invasive PGT

Genetic analysis on **blastocoel fluid** or **spent culture media**

At present, niPGT is to be considered in the research phase.
Further studies and validation are needed before considering its widespread use in clinical practice.





Non-invasive PGT is currently not recommended for routine clinical use.

23 Mitochondrial DNA load measurement

The Quiet Embryo Hypothesis: normally developing embryos have a lower metabolism

At present, mitochondrial DNA load measurement is to be considered in the research phase.

Further studies and validation are needed before considering its widespread use in clinical practice.

24 Time-lapse imaging with or without embryo selection software

a more stable environment

using various morphokinetic parameters, such as the timing of cell divisions and intervals between cell cycles**, improve LBR and time-to-PR**

- (ESHRE Working group on Time-lapse technology et al., 2020).

Efficacy

A Cochrane systematic review and meta-analysis:
No evidence of benefit on LBR or miscarriage rate

Safety

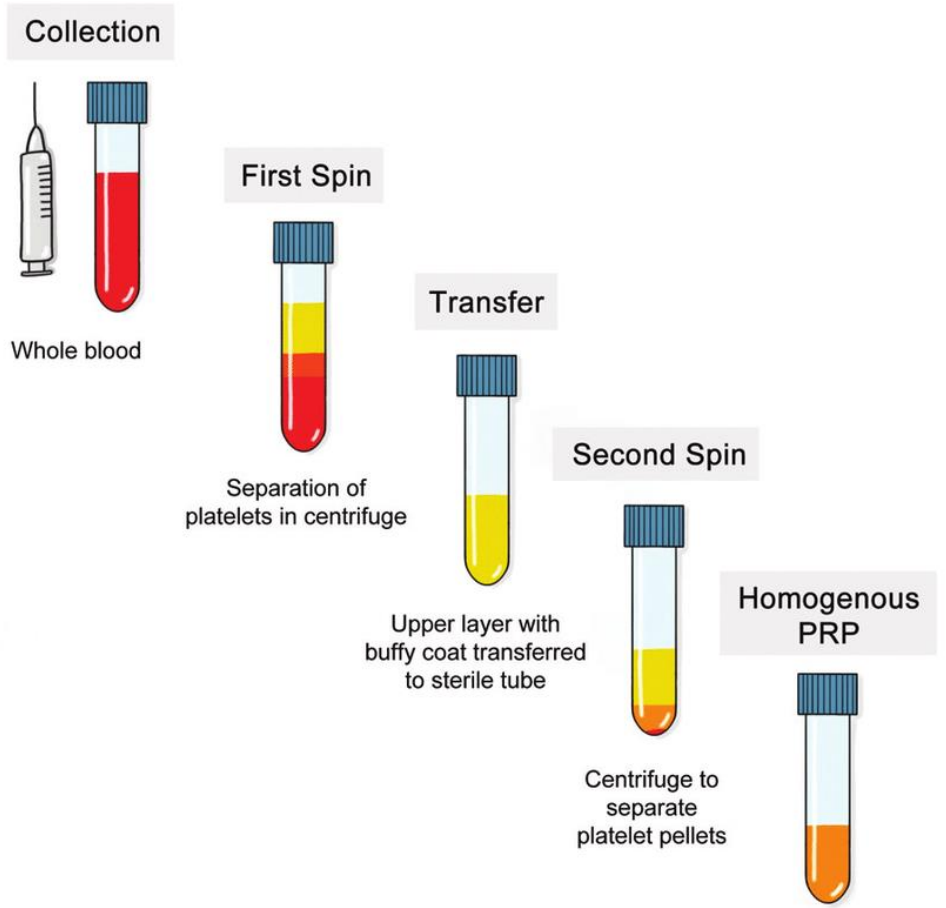
No evidence or rationale for harm

Intrauterine administration of PRP for thin endometrium or RIF

increase cell mitosis, angiogenesis, chondrogenesis, and chemotaxis or stimulate proliferation and growth.

In the context of infertility, it has been hypothesized that PRP may improve **folliculogenesis** and/or **endometrial development**.

PRP is administered as an intrauterine infusion for women with thin endometrium or RIF and as an intraovarian injection in women with **poor ovarian response or POI**.



25 Intrauterine administration of PRP for thin endometrium or RIF

Efficacy

In a systematic review, including three RCTs and four cohort studies involving women undergoing IVF/ICSI, a significantly higher probability of CPR was reported with PRP as compared to controls receiving no, or another, active intervention (RR 1.79; 95% CI 1.37 to 2.32; 7 studies; n = 625; $I^2 = 16\%$; $P < 0.001$) (Maleki-Hajiagha *et al.*, 2020). There was no difference between women who received PRP and women without intervention regarding miscarriage (RR 0.72; 95% CI 0.27 to 1.93; 3 studies; n = 217; $I^2 = 0\%$; $P = 0.51$). More recently published RCTs reported either no difference between groups (Dieamant *et al.*, 2019; Javaheri *et al.*, 2020) or beneficial results on CPR (Nazari *et al.*, 2020; Bakhsh *et al.*, 2022; Nazari *et al.*, 2022a), OPR (Zamaniyan *et al.*, 2021), or LBR (Nazari *et al.*, 2022b) in favour of PRP. While, overall, published data support the use of PRP as an alternative treatment strategy for women with thin endometrium and RIF, it should be acknowledged that studies involved small sample sizes, heterogeneous patient populations and there is a possible overrepresentation of one research group in the data (Nazari *et al.*, 2019, 2020, 2022b). Also, the largest RCT including 438 patients has been registered as aiming to include 30 patients per arm and eventually published with a more than 10 times higher sample size (Nazari *et al.*, 2022b). Owing to the low-quality evidence and the lack of a proper multicentre RCT, it is unclear whether intrauterine PRP has a role in refractory or thin endometrium, or in cases of RIF.

Safety

The use of PRP in other fields of medicine has not been associated with any safety issues or risks. However, no safety evidence exists regarding the exposure of embryos in an endometrial cavity following PRP injection (and the related growth factors). In addition, no safety evidence exists regarding the potential short- or long-term effects of injection of PRP in the uterus.

Recommendation

While the available data regarding intrauterine PRP in the context of ART show promise, it is important to acknowledge the significant issues related to their quality and the overall lack of safety data. Further investigation and well-designed studies are necessary to assess the efficacy and ensure the safety of this procedure before considering its use in routine clinical practice.

26 Intraovarian PRP injection for poor ovarian response or premature ovarian insufficiency

➢ Efficacy

no RCTs have been published regarding the potential role of intraovarian PRP injection in women with POI or poor ovarian response.

A systematic review of four studies (one case-control and 3 uncontrolled studies involving 696 women) concluded that intraovarian PRP infusion **increases the mature oocyte yield, fertilization rates, and good-quality embryo formation rate**

➢ Safety

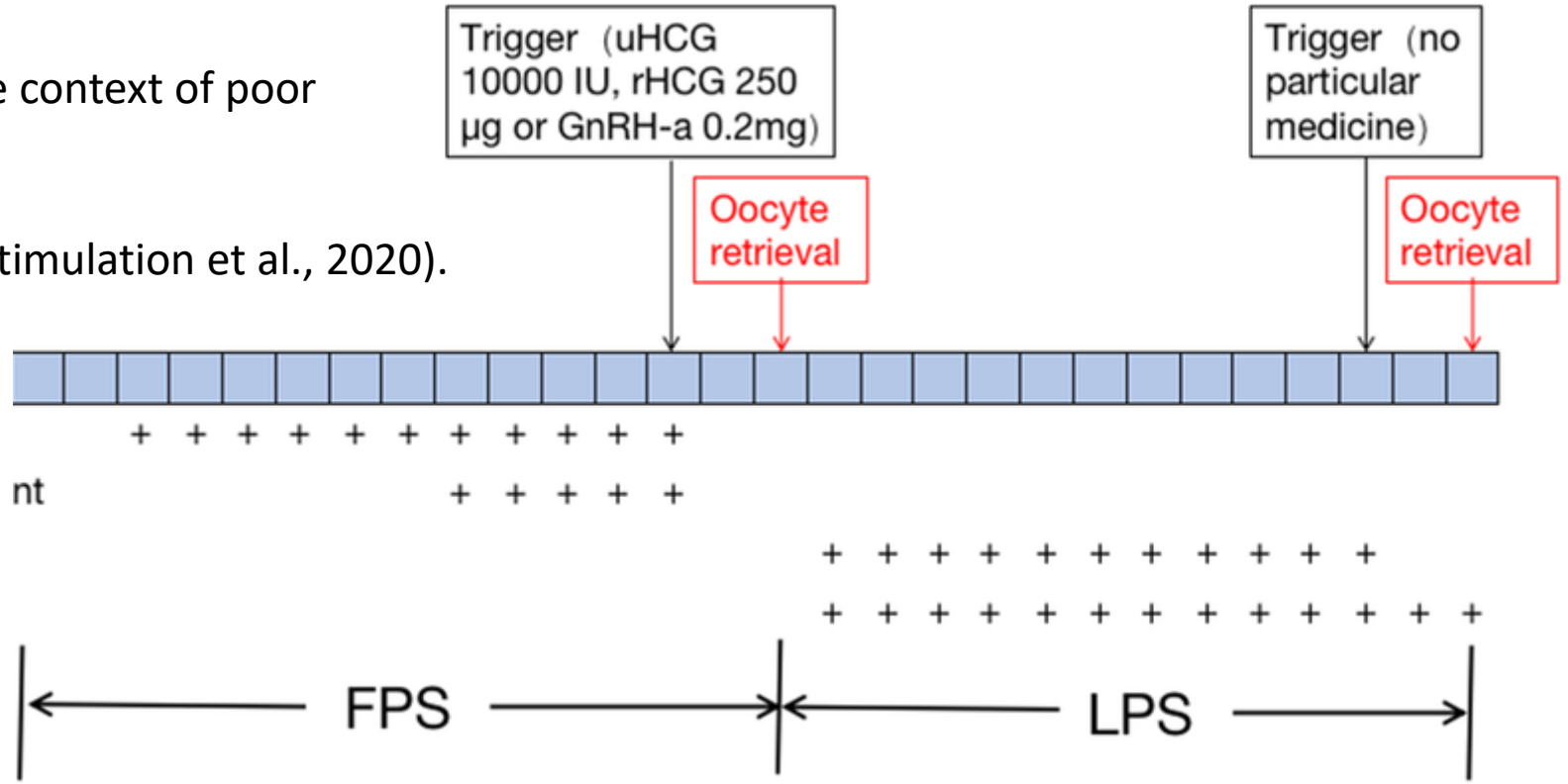
Currently, there is a lack of RCTs or controlled studies that demonstrate the efficacy of intraovarian PRP. Furthermore, the available data regarding the safety of intraovarian PRP in the context of ART are limited. Further investigation and well-designed studies are necessary to assess its efficacy and ensure its safety before considering its use in routine clinical practice.

27 Double stimulation or 'Shanghai protocol

the retrieval of more oocytes in a shorter time and has been used mainly for **poor responders** and (urgent) **fertility preservation patients**.

further research is needed, particularly in the context of poor responders

- (The ESHRE Guideline Group on Ovarian Stimulation et al., 2020).



Duostim is currently **not** recommended for **routine clinical use**.

28 Adjuncts during ovarian stimulation

- (The ESHRE Guideline Group on Ovarian Stimulation et al., 2020).

The authors did not find any relevance for the addition of the following compounds before and/or during ovarian stimulation: **metformin, growth hormone, testosterone, dehydroepiandrosterone (DHEA), aspirin, indomethacin, and sildenafil**. For some compounds, available data showed no benefit, while for others (indomethacin, and sildenafil) no studies have been performed. Safety data are lacking for most of these compounds.

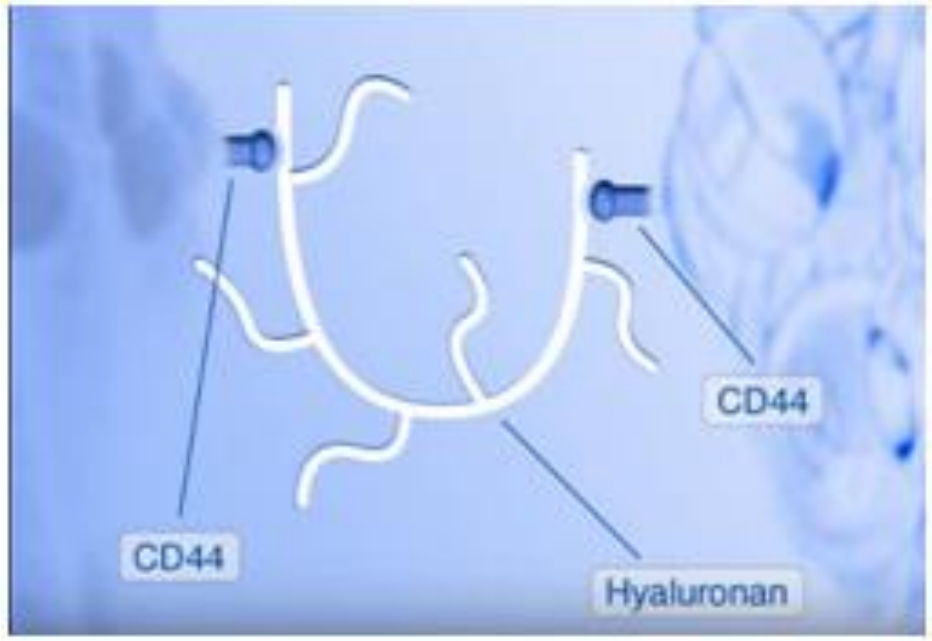
However, the use of these adjuncts based on **individual patient characteristics or in specific clinical circumstances** may warrant further investigation

Intravaginal and intrauterine culture device

Given the limited quality of the available information, there is insufficient evidence to support the use of intravaginal or intrauterine culture devices as a substitute for standard IVF treatment in terms of clinical outcomes and efficacy. Further investigation and well-designed studies are necessary to assess the efficacy of these devices.

30 Additions to transfer media (hyaluronic acid)

HA is one of the major macromolecules present in the female reproductive tract, and has been shown to increase in the uterus at the time of implantation in humans



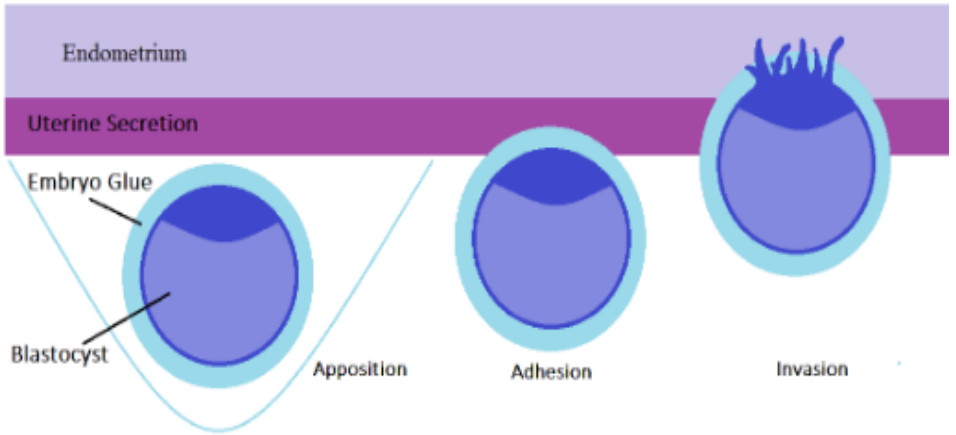
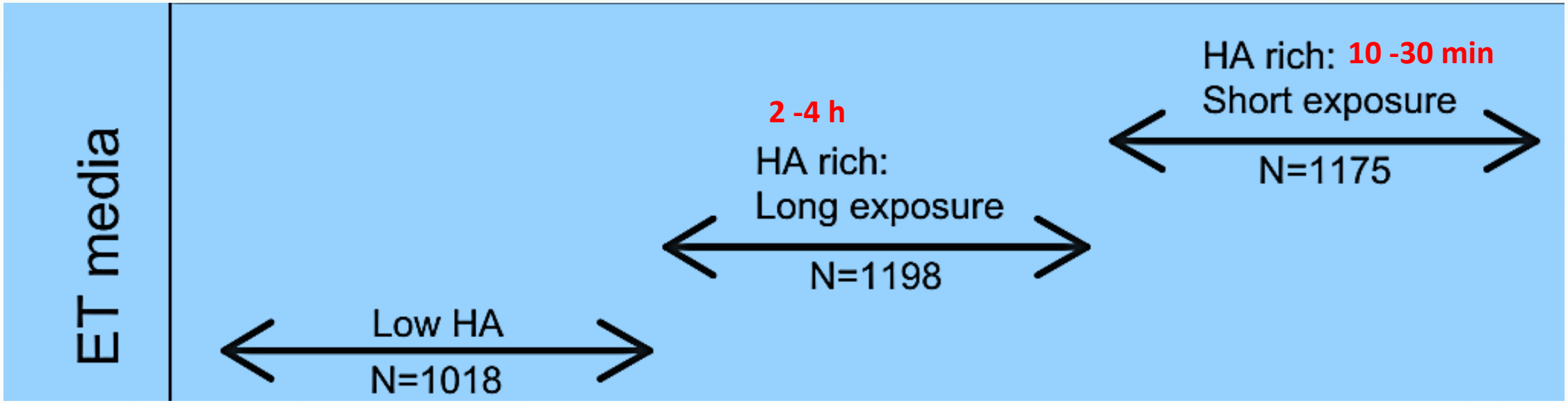


Fig: Embryo transferred with Embryo glue

Embryo Transfer: hyaluron- containing embryo transfer medium



The use of HA-rich medium for ET was **positively** and **significantly** associated with improved clinical pregnancy rate and LBE, for both exposure durations

Adeniyi, 2021

Additions to transfer media (hyaluronic acid)

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

Hyaluronic acid in embryo transfer media for assisted reproductive technologies

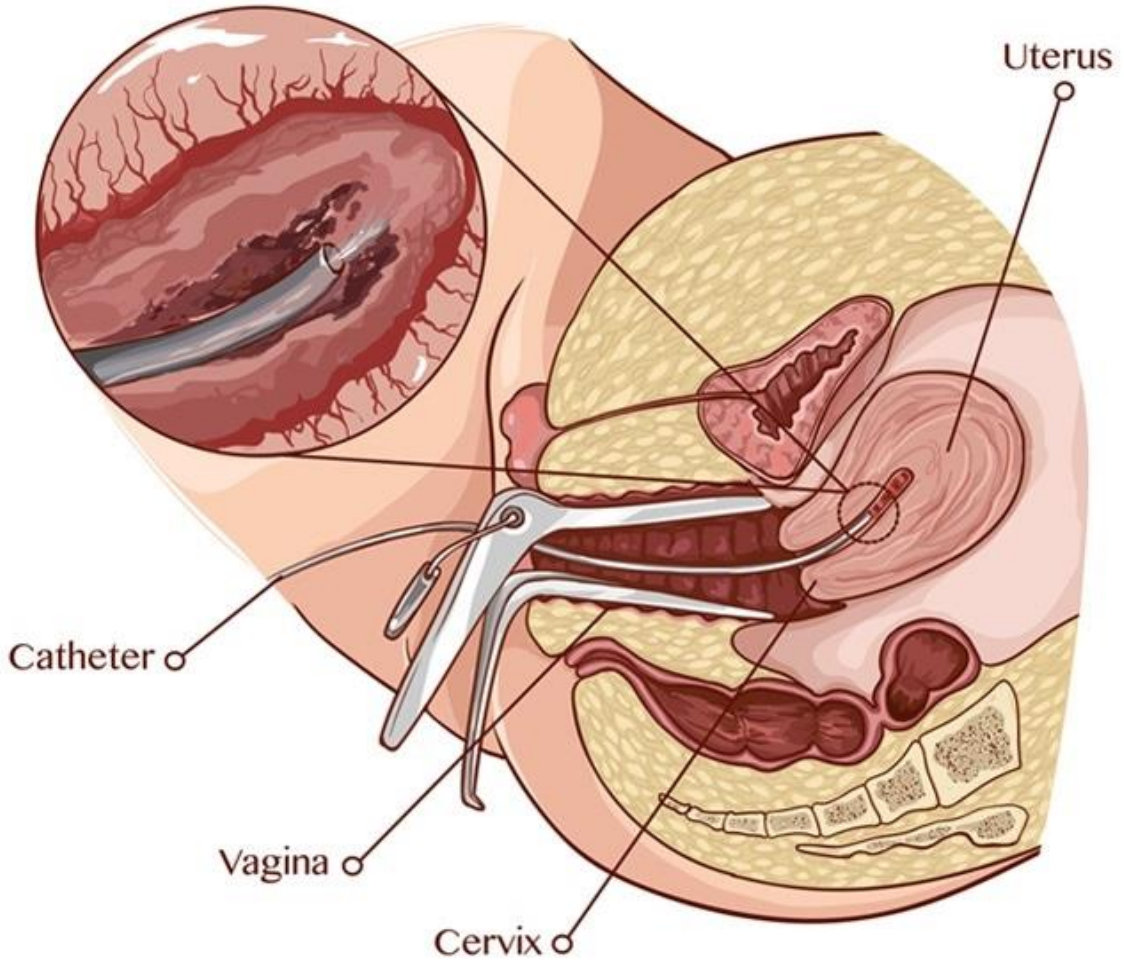
Devorah Heymann[1], Liat Vidal[2], Yuval Or[1,3], Zeev Shoham[1,3,4]

Hyaluronic acid addition to transfer media **is recommended**.

Monitoring of the multiple pregnancy rate is still advisable.

31 Endometrial scratching

This hypothesis is based on the potential of induction of endometrial decidualization, the triggering of a wound-healing response, associated with a beneficial '**inflammatory response**' in the endometrium, the modulation of gene expression involved in the **preparation of the endometrium for embryo implantation**



31 Endometrial scratching

Cochrane systematic review and meta-analysis included a total of 37 RCTs (8786 women). The effect of endometrial scratching on **LBR was unclear** as the result was consistent with **no effect, a small reduction, or an improvement**

- **Safety**

Minimal to moderate bleeding and pain may occur about endometrial scratching.
When the procedure is performed by hysteroscopy, there is a small risk of infection.

Recommendation: still uncertainty regarding the effect of endometrial scratching on LBR owing to large **heterogeneity** among studies in methodology and timing of the intervention.

Subgroup analyses also failed to identify patient groups that would benefit from endometrial scratching.

Endometrial scratching is currently not recommended for routine clinical use.

Flushing of the uterus

32  **Intrauterine administration of hCG is not recommended**

33  **Intrauterine administration of G-CSF**

34  **Endometrial administration of embryo culture supernatant**

35  **Endometrial exposure to seminal plasma**

Stem cell mobilization

36

Stem cell therapy for **premature ovarian insufficiency** or **diminished/poor ovarian reserve**

37

Stem cell therapy for **thin endometrium**

The **biological rationale** for stem cell therapy is unclear.
The available data on efficacy are limited and primarily derived from observational studies with **small sample sizes**.
There are serious safety concerns with this technique. Further preclinical studies are necessary to assess the relevance and potential efficacy of this technique.

38 Steroids

✓ *Steroids are used in women with **autoimmune diseases**, even before or during treatment, but this is **not considered an add-on treatment**.*

As add-ons:

- Cochrane systematic review and meta-analysis reported that the LBR was comparable across groups assigned to **glucocorticoid** supplementation (different dosages) or placebo.

- A meta-analysis of women undergoing IVF treatment reported that CPR was not different in women using glucocorticoids and those who did not (Achilli et al., 2018).

➢ **Safety**

animal studies: cardiovascular, metabolic, neuroendocrine disorders, and teratogenic effects.
In humans, increased risk of **miscarriage, preterm births, gestational hypertension, and diabetes** have been reported, even if the data are limited (Kim, 2021).

➢ While there is some indication of **potential benefits in patients with autoimmune disease**, it is important to note that the existing data on the use of glucocorticoids in ART is limited and based on small, non-controlled studies with inconsistent criteria.

Elective freeze-all

✓ *It is still considered a valid preventative strategy for OHSS*

➢ **Efficacy**

Four large cohort studies based on the SART, HFEA and Victoria (Australia) data have shown the same tendency that the freeze-all strategy seems to be beneficial in high responders but not in **intermediate or low responders.**

Cochrane systematic review and meta-analysis found little or no difference in cumulative LBR between the 'freeze-all' strategy and the conventional fresh ET

➢ **Safety**

Cochrane review showed that the risks of hypertensive disorder in pregnancy (HDP) and large for-gestational age were higher after the freeze-all strategy than after fresh ET and also a higher mean birthweight was observed after freeze-all.

39 Elective freeze-all

➢ **Recommendation**

the cumulative LBR and LBR with the freeze-all strategy are not superior to fresh ET, while the time to achieve pregnancy is likely to be longer.

Elective freeze-all carries obstetric and perinatal risks such as **hypertensive disorders in pregnancy,** large for gestational age, and macrosomia.

The freeze-all strategy should only be considered when there is a clear clinical indication, such as a higher risk of **OHSS or endometrial pathology**, and in cases involving **PGT**. Adopting the freeze-all strategy should be done judiciously, considering individual patient factors and the potential risks involved.

ICSI for non-male factor infertility

Despite the stable incidence of male factor infertility over the last decades, the use of ICSI increased from 35% of all ART cycles in 1997 to >70% in 2018

Is ICSI Worth the Investment in Non-Male Factor Infertility?

- Studies in poor ovarian responders and advanced maternal age patients did not demonstrate improved outcomes with ICSI.

- Some studies reported lower LBRs with ICSI in patients with advanced maternal age.

- Recent RCTs showed comparable fertilization rates, fertilization failure, and LBRs between IVF and ICSI.

Safety Concerns and Outcomes of ICSI vs. IVF

➢ **Perinatal and Neonatal Outcomes:**

Concerns were raised about the safety of ICSI compared to IVF, with reports suggesting associations between perinatal/neonatal outcomes and paternal characteristics linked to male factor infertility.
However, a large **retrospective study** in 2020, a meta-analysis including **46 studies**, and a recent **RCT** (>1000 patients) found **no significant differences in perinatal outcomes between ICSI and IVF treatments**.

➢ **Long-Term Child Development:**

•Early studies suggested potential delayed development in children born after ICSI, but later reports and systematic reviews indicate no significant differences in **neurodevelopment, growth, vision, and hearing** between ICSI and spontaneously conceived children.
•The clinical significance of general physical health and **metabolic/reproductive endpoints** remains unclear and requires further investigation.

Safety Concerns and Outcomes of ICSI vs. IVF

➢ **Imprinting Disorders and DNA Methylation:**

•Initial studies suggested higher DNA methylation in an imprinted gene for children born from ICSI, but a meta-analysis in 2014 found insufficient evidence for an association between ART (including ICSI) and methylation in other imprinted genes.

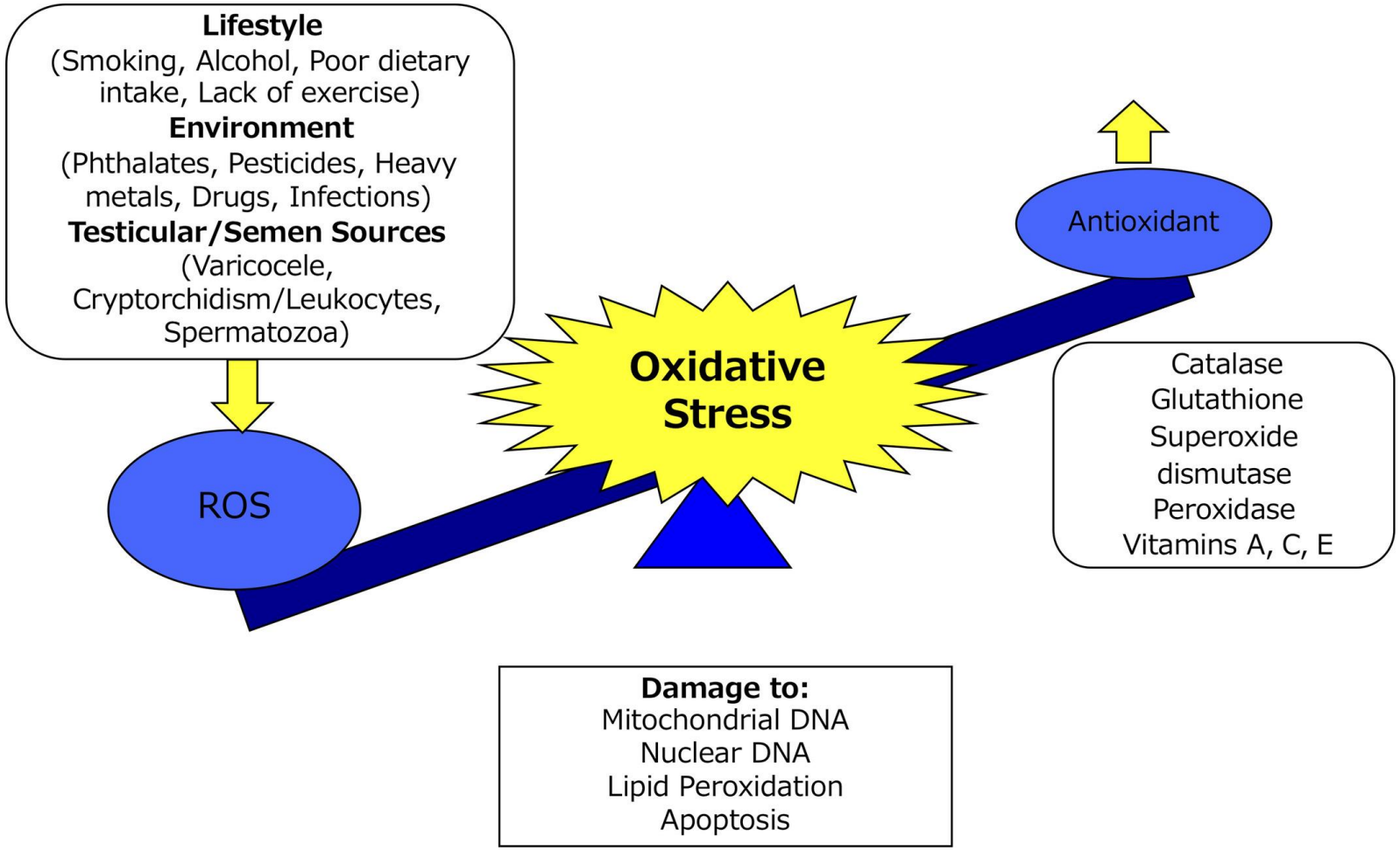
•Recent evidence suggests that ART, including ICSI, is associated **with limited epigenetic variation** at birth, **mostly resolving by adulthood**.

Consideration of Data Source:

•Most data comes from studies involving patients with male factor infertility, making it challenging to determine whether recorded defects are related to ICSI or the underlying infertile condition itself.

ICSI is not recommended for non-male factor infertility

Antioxidant therapy



41 Antioxidant therapy

Female Subfertility:

•Cochrane systematic review on oral antioxidants (1–3 cycles) for female subfertility found uncertainty in improving LBR compared with placebo or standard treatment.

•Limited evidence (very low-quality) indicated a small overestimation of the antioxidant effect on **LBR**, but no significant difference in miscarriage rates.

•**No specific type of antioxidant** was found to be superior to others.

41 Antioxidant therapy

Male Subfertility:

•Cochrane review on oral antioxidants (3-12 months) for male subfertility suggested a potential increase in LBR compared to placebo or no treatment (**very low-quality evidence**).
•Removing studies **at high risk of bias** showed no evidence of increased live birth, and no increased risk of miscarriage was observed.
•No significant differences were found among different antioxidants.

Patient Stratification Studies:
•Several studies aimed to identify specific patient groups benefiting from antioxidant therapy based on BMI, smoking, lifestyle factors, basal DFI, and varicocele presence.
•Limitations included small sample sizes, retrospective designs, varied antioxidant combinations, and the use of surrogate parameters (semen parameters or DFIs) instead of Pregnancy Rate

41 Antioxidant therapy

Recommendation

Antioxidant therapy lacks substantial and reliable evidence demonstrating a significant enhancement in LBRs

Complementary and alternative medicine

Acupuncture, nutritionist services, Chinese herbal medicine (CHM), mindfulness, hypnotherapy, massage, yoga, meditation, and detoxing

In ART, fertility clinics often promote complementary therapies, suggesting they can enhance patient relaxation, well-being, and potentially improve IVF outcomes.

According to a UK patient survey by the HFEA, **acupuncture** ranked as the second most common IVF add-on (HFEA, 2018).
Similarly, an Australian study identified **acupuncture** and **Chinese Herbal Medicine** (CHM) among the top three ART add-ons (Lensen et al., 2021a).

Notably, practitioners offering complementary therapies in the UK are typically external to the IVF unit, leading to limited control over the information provided to patients by clinics.

Complementary and alternative medicine

1.Evaluating complementary therapies in ART through RCTs is challenging due to diverse control group choices and inconsistent methodologies across studies, particularly in acupuncture interventions.

2.Recent meta-analyses on acupuncture show varying results, with some indicating **no significant** effect on LBR or CPR, accompanied by low-quality evidence and method heterogeneity.

3.Herbal medicine, especially Chinese Herbal Medicine, has shown potential benefits in increasing LBR and CPR, but there is a call for **additional RCTs** with robust methodology and long-term follow-up. L

Acupuncture, Chinese and herbal medicine and other complementary therapies are not recommended.

Out of 42 interventions assessed,

none could be based on high-quality evidence,

and **only four on moderate-quality evidence**.

In essence, **95% of the recommendations hinge on low-quality sources**.

Selling Hope to patients