



**Coppie che hanno provato di tutto e hanno fallito tutto, è giunto il tempo di proporre la "doppia donazione di gameti"?**

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# Questions

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- Couples who have tried everything, what is everything?
- Couples who have failed everything, what does it mean to fail everything?
- What are the indications for the use of donor gametes?

## Everything?

## Time invested

4-6 IUI	8 months
+	
3 IVF with 4-5 TRF	12 months
+	
1 IVF with PGT-A	2 months
+	
1 egg or sperm donation cycle	3 months

## Everything?

4-6 IUI	8 months
+	
3 IVF with 4-5 TRF	12 months
+	
1 IVF with PGT-A	2 months
+	
1 egg or sperm donation cycle	3 months

## Time invested

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**25 months**

# Have been or one all, include "add ons"?

Table 2. Overview of all recommendations on diagnosis and diagnostic tests with their level of evidence, benefit versus harm and other considerations that contributed to their formulation.

Intervention	Benefit versus harm (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR) <sup>1</sup>	Level of evidence for safety <sup>1</sup>	Considerations	Recommendation
<b>Screening hysteroscopy</b>	Unselected patients: no benefit on LBR. RIF might be beneficial effect on LBR. No evidence of an effect on miscarriage rate. Complications are minimal.	⊕⊕○○	⊕⊕○○	/	Screening hysteroscopy is <b>currently not recommended for routine clinical use</b> . Screening hysteroscopy can be considered in patients with recurrent implantation failure.
<b>Endometrial receptivity tests</b>	No effect on LBR, inconclusive effect on cLBR. No data on safety, biopsies procedure can be painful.	⊕⊕○○	No data	Clinical and methodological heterogeneity in patient populations (number of previously failed cycles), reported comparisons and unit of analysis (per couple or per cycle).	The presently available endometrial receptivity tests are <b>not recommended</b> .
<b>Immunology tests and treatments</b>	Immunology tests: Benefits on LBR or miscarriage rate is unclear due to lack of understanding of the mechanisms. Harms: misinformation.	⊕○○○	No data	No rationale for these tests, no standardization.	Peripheral blood tests for immune parameters and uNK-cell testing are <b>not recommended</b> . KIR and HLA genotyping is <b>currently not recommended for routine clinical use</b> .
	Immunology treatments: Benefits on LBR and miscarriage rate are unclear. Significant safety concerns.	⊕⊕○○	No data	No rationale for these treatments, no standardization.	Immunomodulating treatments, such as Intralipid, IVIG, Rh-1IF, PIMCs, and anti-TNF are <b>not recommended</b> .

Table 5. Overview of all recommendations on clinical management with their level of evidence, benefit versus harm and other considerations that contributed to their formulation.

Intervention	Benefit versus harm (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR) <sup>1</sup>	Level of evidence for safety <sup>1</sup>	Considerations	Recommendation
<b>Follicle-stimulating plasma</b>	Intrauterine FFP administration: Evidence of benefits on CFR, no evidence of an effect on miscarriage rate. No evidence of harm.	⊕○○○	⊕○○○	Current studies include a small sample size and heterogeneous study population in addition to different dosages of FFP.	Intrauterine administration of platelet-rich plasma is <b>not recommended</b> .
<b>Duostim</b>	Intrauterine FFP administration: Mostly uncontrolled studies, no data on effect on LBR or miscarriage rate. No evidence of harm.	No data	No data	As RCT comparing duostim with two conventional stimulations has not been performed to date.	Duostim is <b>currently not recommended for routine clinical use</b> .
<b>Adjuncts during ovarian stimulation</b>	Conflicting evidence on LBR safety concerns.	⊕⊕○○	⊕⊕○○	/	Adjuncts (metformin, growth hormone, testosterone, DHEA, aspirin, indomethacin, and sildenafil) before or during ovarian stimulation are <b>not recommended</b> .
<b>Intrauterine and intravaginal culture device</b>	Intrauterine culture device: No evidence of a benefit on LBR. No data on harms. Intrauterine culture device: One small study showing no benefit on LBR. No data on harms.	⊕○○○	No data	An embryo bag and an IVF lab are still required.	Intrauterine and intravaginal culture devices are <b>currently not recommended for routine clinical use</b> .
<b>Additions to transfer media (HA)</b>	With a high dose of HA, a benefit on LBR and reduced risk of miscarriage was found. Complications: increased multiple pregnancy rate.	⊕⊕⊕○	⊕⊕⊕○	The use of HA should be combined with a single embryo transfer policy.	Hyaluronic acid addition to transfer media is <b>recommended</b> . Monitoring of the multiple pregnancy rate is still advisable.
<b>Endometrial scratching</b>	Inconclusive data on benefit on LBR, with no effect on miscarriage rate. Complications: moderate pain, bleeding, risk of infection.	⊕⊕⊕○	⊕⊕⊕○	Timing of scratch and methodology of the procedure differed between studies.	Endometrial scratching is <b>currently not recommended for routine clinical use</b> .
<b>Flushing of the uterus</b>	Intrauterine administration of hCG: Some benefit for cleavage stage (not blastocyst) transfer at >500 IU. No evidence of harm. Intrauterine administration of G-CSF: No evidence of benefit on LBR. This endometrium may improve LBR in RCT. Very few side effects reported. Endometrial administration of embryo culture supplement: No evidence of benefit on LBR or miscarriage rate. No evidence of harm.	⊕⊕⊕○	⊕○○○	Timing of administration, dosage of hCG and timing of embryo transfer differed between studies.	Intrauterine administration of hCG is <b>not recommended</b> . Intrauterine administration of granulocyte colony-stimulating factor is <b>not recommended</b> . Endometrial administration of embryo culture supplement is <b>not recommended</b> .

Table 4. Continued

Intervention	Benefit versus harm (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR) <sup>1</sup>	Level of evidence for safety <sup>1</sup>	Considerations	Recommendation
<b>MACS</b>	No evidence of benefit on LBR or miscarriage rate. No harms reported.	⊕○○○	⊕○○○	/	Magnetic-activated cell sorting is <b>currently not recommended for routine clinical use</b> .
<b>Microfluidics</b>	Only one RCT reporting benefit on LBR. No harms reported.	⊕⊕○○	No data	/	Microfluidics for sperm selection and preparation can be considered.
<b>IMSI</b>	No evidence of benefit on LBR or miscarriage rate. No complications reported.	⊕○○○	⊕○○○	The method of IMSI can be time-consuming and impacts laboratory workflow.	Intracytoplasmic morphologic sperm injection is <b>currently not recommended for routine clinical use</b> .
<b>Growth factor supplemented embryo culture medium</b>	No evidence of benefit on LBR or miscarriage rate. Theoretical harms, but not reported.	⊕⊕○○	⊕⊕○○	As growth factors act in both positive and negative synergy to produce an effect, addition of a single growth factor to embryo culture media is questionable and will not necessarily elicit a beneficial effect.	Growth factor-supplemented embryo culture medium is <b>not recommended</b> .
<b>Assisted hatching</b>	No evidence of benefit on LBR or miscarriage rate. Complications: increased multiple pregnancy rate.	⊕⊕○○	⊕○○○	/	Assisted hatching is <b>not recommended</b> .
<b>Genetic testing and treatments</b>	PCT-A: Most RCTs did not report benefit on LBR, but some suggest reduced miscarriage rate. Harms include disposal of viable embryos and IVIC. nIPT-A: No data regarding effect on LBR or miscarriage rate. Considered to be safer than PCT-A. Mitochondrial DNA load measurement: No data regarding effect on LBR or miscarriage rate. Expected complications are similar to PGT-A.	⊕⊕○○	⊕○○○	Lack of standardization in biopsy and analysis method.	Pre-implantation genetic testing for aneuploidy is <b>currently not recommended for routine clinical use</b> .
<b>Time-lapse imaging</b>	No evidence of benefit on LBR or miscarriage rate. No evidence or rationale for harm.	⊕⊕○○	No data	/	Time-lapse imaging is <b>not recommended</b> as a tool to improve live birth rates.

Table 5. Continued

Intervention	Benefit versus harm (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR) <sup>1</sup>	Level of evidence for safety <sup>1</sup>	Considerations	Recommendation
<b>Endometrial exposure to seminal plasma</b>	No evidence of a benefit on LBR or miscarriage rate. Complications: no evidence of an effect on multiple pregnancy rate, potential risk of allergic reaction.	⊕○○○	⊕○○○	Available evidence is very heterogeneous with regard to the inclusion/exclusion criteria of patients, and the interventions.	Endometrial exposure to seminal plasma is <b>not recommended</b> .
<b>Stem cell mobilization</b>	Stem cell therapy for PCO or DOR: Available evidence comes from case reports and uncontrolled studies with very little information on the actual procedures and long-term follow-up is lacking. Stem cell therapy for endometriosis: No benefit on LBR/CPR. Safety concerns: increased risk of miscarriage, pyogenic boritis, gestational hypertension, ...	No data	No data	/	Stem cell therapy for premature ovarian insufficiency, diminished/poor ovarian reserves or thin endometrium is <b>not recommended</b> .
<b>Elective freeze-all</b>	No benefit on LBR of freeze-all over fresh transfer. Complications: higher risk of hypertensive disorder in pregnancy, larger gestational age, and higher newborn birth weight.	⊕⊕⊕○	⊕⊕⊕○	With similar LBR and CPR and longer time to pregnancy and the added freezing/thawing procedures the cost with a "freeze-all" for all strategies will exceed the costs in conventional fresh embryo transfer.	Elective freeze-all is <b>currently not recommended for routine clinical use</b> .
<b>ICSI for non-male factor infertility</b>	Conflicting evidence of effect on LBR, even if most studies report no significantly higher LBR with ICSI. Safety is similar to IVF.	⊕⊕○○	⊕⊕○○	Mean laboratory time is significantly longer for ICSI compared to conventional IVF, in addition to an increase in cost.	ICSI is <b>not recommended</b> for non-male factor infertility.
<b>Antioxidant therapy</b>	Effect on LBR in females is uncertain, no evidence of effect on LBR in males, no evidence of effect on miscarriage rate. Complications: gastrointestinal discomfort has been reported.	⊕○○○	⊕⊕○○	Most of the studies showed a small sample size, retrospective design, used various combinations of antioxidants and serum parameters or DEI were used as surrogate success parameters rather than pregnancy rate.	Antioxidant therapy is <b>not recommended</b> in ART treatment.
<b>Complementary and alternative medicine</b>	Acupuncture: Conflicting evidence of effect on LBR, no evidence of effect on miscarriage rate. Minor adverse effects have been reported. Other complementary therapy: No data. Alternative medicine: May improve LBR/CPR. No data regarding safety.	⊕⊕○○	⊕○○○	Assessing complementary therapies through RCTs is challenging, especially with respect to a suitable control group and consistent methodology.	Acupuncture, Chinese and herbal medicine and other complementary therapies are <b>not recommended</b> .

Table 4. Overview of all recommendations on laboratory tests and interventions with their level of evidence, benefit versus harm and other considerations that contributed to their formulation.

Intervention	Benefit versus harm (efficacy versus safety)	Level of evidence for efficacy (LBR/CPR) <sup>1</sup>	Level of evidence for safety <sup>1</sup>	Considerations	Recommendation
<b>Artificial oocyte activation</b>	Beneficial in patients with previous fertilization failure or low fertilization rate and embryo developmental problems. Safety to be considered (mechanism unclear), but not reported.	⊕⊕○○	⊕⊕○○	Current studies show variation in ionophore stimulus with respect to concentration, exposure time, and number of exposures.	Artificial oocyte activation is <b>currently not recommended for routine clinical use</b> . Artificial oocyte activation is recommended for complete activation failure (CF, ZPN), very low fertilization (CFN) fertilization, or oligo-asthenozoospermia.
<b>Mitochondrial replacement therapy</b>	Few data, no benefit on LBR. No data on safety.	⊕○○○	No data	In some cases, the acceptor's mtDNA haplotype takes over the donor's mtDNA.	Mitochondrial replacement therapy to affect oocyte quality is <b>not recommended</b> .
<b>In vitro activation of dormant follicles</b>	No comparative studies. Safety, adverse effects, and long-term effects: no data.	⊕○○○	No data	For PCO patients, options are limited.	In vitro activation of dormant follicles is <b>not recommended</b> .
<b>IVM</b>	Clinical IVM: No comparative studies. Abnormal fertilization and developmental arrest reported. Rescue IVM: LBR is lower, effect on miscarriage rate is unclear, most studies report increased miscarriages/decreased implantation. Safety of rescue IVM is questionable, since these oocytes commonly have meiotic defects and are of poor quality.	⊕○○○	No data	It has been suggested that IVM encompasses a lower financial and emotional burden as compared to standard IVF/ICSI.	Clinical IVM and rescue IVM or partial cycle IVM are <b>currently not recommended for routine clinical use</b> .
<b>Sperm DNA testing and treatment</b>	Diagnostic potential, inconclusive. No adverse events reported.	⊕○○○	No data	Different assays have different discriminatory capacity. Different lab conditions and sperm source can influence the outcome of the test.	Sperm DNA damage testing is <b>currently not recommended for routine clinical use</b> .
<b>Artificial sperm activation</b>	Higher LBR/CPR. No data on safety. Malformations reported in animal studies.	⊕○○○	⊕○○○	/	Artificial sperm activation is <b>currently not recommended for routine clinical use</b> . Artificial sperm activation is recommended for patients with primary or secondary testicular azoospermia which are not the result of structural structure defects.
<b>Sperm evaluation and selection</b>	Hyaluronic acid binding assay and physiological ICSI: No evidence of benefit on LBR, reduced miscarriage rate. No harms reported.	⊕○○○	No data	Hyaluronic acid binding assay has limited standardization.	Sperm hyaluronin binding assay is <b>currently not recommended for routine clinical use</b> . Physiological ICSI is <b>currently not recommended for routine clinical use</b> .



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 ESHRE Pages

## Good practice recommendations on add-ons in reproductive medicine<sup>†</sup>

ESHRE Add-ons working group: K. Lundin<sup>1</sup>, J.G. Bentzen<sup>2</sup>, G. Bozdag<sup>3</sup>, T. Ebner<sup>4</sup>, J. Harper<sup>5</sup>, N. Le Clef<sup>6</sup>, A. Moffett<sup>7</sup>, S. Norcross<sup>8</sup>, N.P. Polyzos<sup>9</sup>, S. Kautakallo-Hokkanen<sup>10</sup>, I. Sfountouris<sup>11</sup>, K. Sermon<sup>12</sup>, N. Vermeulen<sup>13</sup>, and A. Pinborg<sup>14</sup> <sup>1-14</sup>



# Success or Failure “Health care quality dimensions”

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## Safety

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- Avoid any medical-surgical therapy or diagnostic procedures that represent a foreseeable risk when alternative options exist
- Reduce the number of diagnostic and therapeutic actions that imply risk
- In all cases the risk must be justified by the expected benefits.

## Effectiveness

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Healthy newborn, with the lowest number of IUI / oocyte aspirations / embryo transfers, in the shortest possible time

## Patient-centeredness

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Informed and shared decision-making. All fertility patients value informed decision-making and some want to take part in decisions after being informed and supported

## Efficiency

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- Lowest possible economic investment
- Shortest possible time
- Avoid changes in the quality of life of patients

# Success or failure?

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A Healthy New Born after:

- Two years after first visit to Fertility Clinic
- Four COH and three OPU
- Five embryo transfers
- A lot of time and money invested

# Indication for use of gamete donation

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- Absence of competent gametes
- Presence of genetic alteration and/or inevitably transmissible pathology
- Woman without a male partner
- Repeated failures without an identifiable cause (?)

# When to offer double donation after repeated failures?

4-6 IUI	8 months
+	
3 IVF with 4-5 TRF	12 months
+	
1 IVF with PGT-A	2 months
+	
1 egg or sperm donation cycle	3 months

After 25 months of treatments and failures, a couple is:

Angry

Distrustful

Tired

...and without money



# When to consider double donation after repeated failures?

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- Donor eggs:  
Low ovarian reserve, advanced age
- Donor sperm:  
Moderate/severe sperm defects, advanced age (?)
- Double gamete donation:  
Both gametes with the previously described defects

# When is the right time to offer a double donation?

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- Individualization of each case
- Repeated low oocyte yield
- Repeated low fertilization and embryo development rate

The first IVF Meeting in our World:  
Bourn Hall 1981. **The pioneers.**



# Thank you!

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