
# Add-ons e medicina personalizzata nel laboratorio PMA. Miti, leggende e superstizioni o realtà?

*Alessio Paffoni*

- Nessun conflitto di interessi sui temi della presentazione
- A.E. Hum Reprod Open
- Membro Comitato Etico 5 Lombardia

# Perché gli add-ons piacciono così tanto?

Riducono l'ansia con la "percezione di controllo".

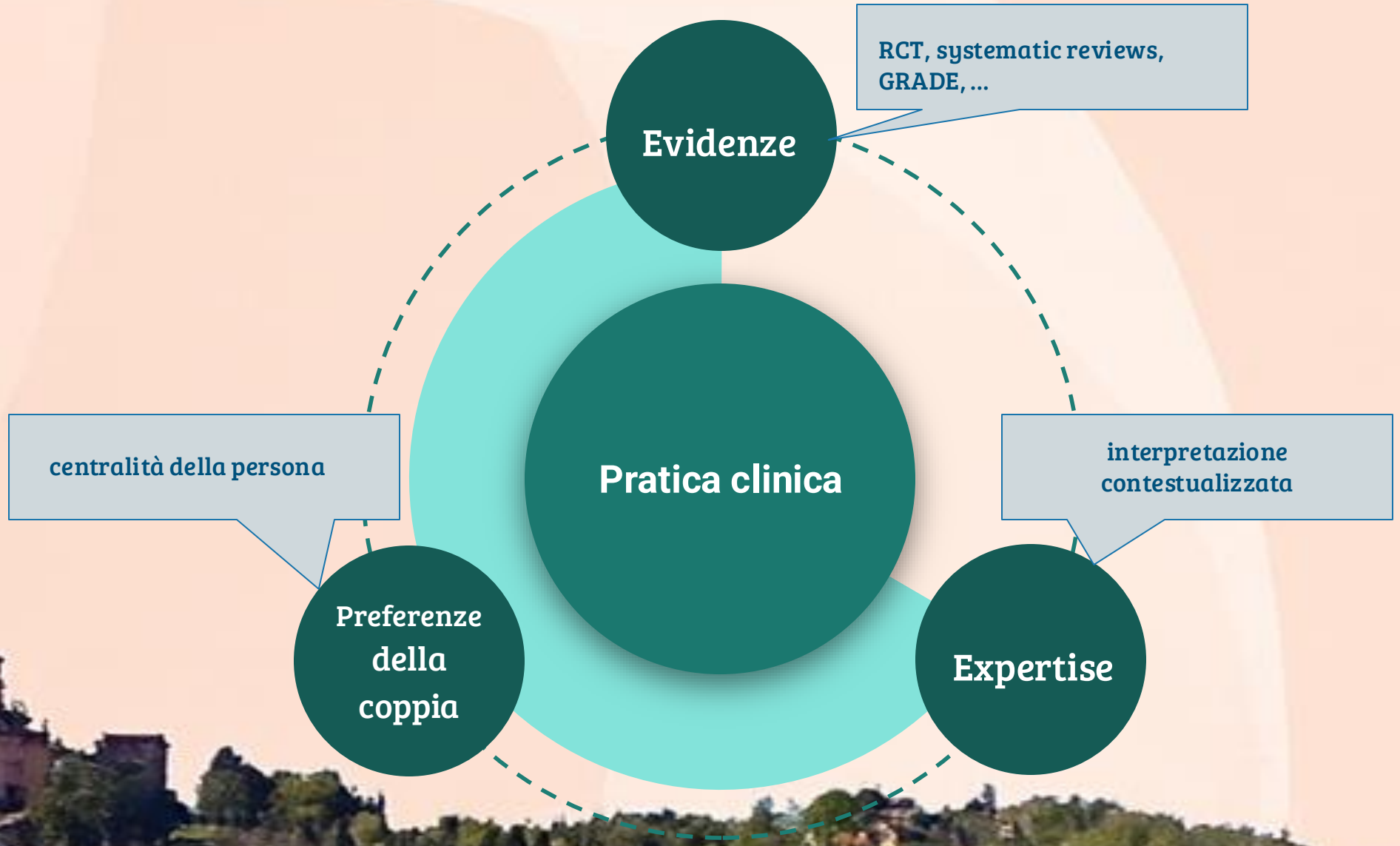
Rassicurano le coppie in un percorso emotivamente difficile ("le abbiamo provate tutte").

Offrono narrazioni semplici ("più tecnologia = più successo").

Spesso rispondono a un bisogno tecnologico, non clinico.

Sono la risposta alla nobile esigenza di cercare di fare avanzare lo stato dell'arte

# Add-ons


Evidenze
RCT, systematic reviews, GRADE, ...
Pratica clinica
centralità della persona
interpretazione contestualizzata
Preferenze della coppia
Expertise

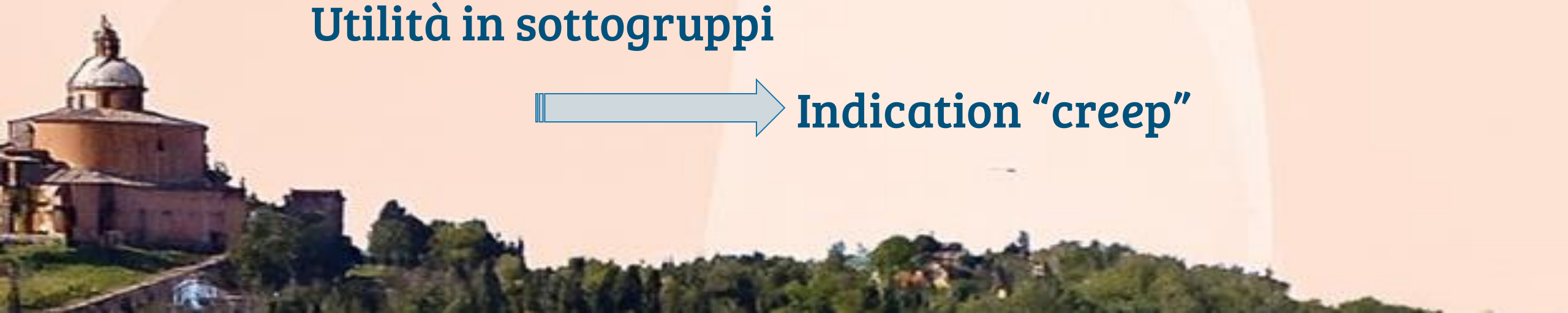
# Pseudo-personalizzazione

Aggiungere non significa personalizzare

Rischio di sovratrattamento

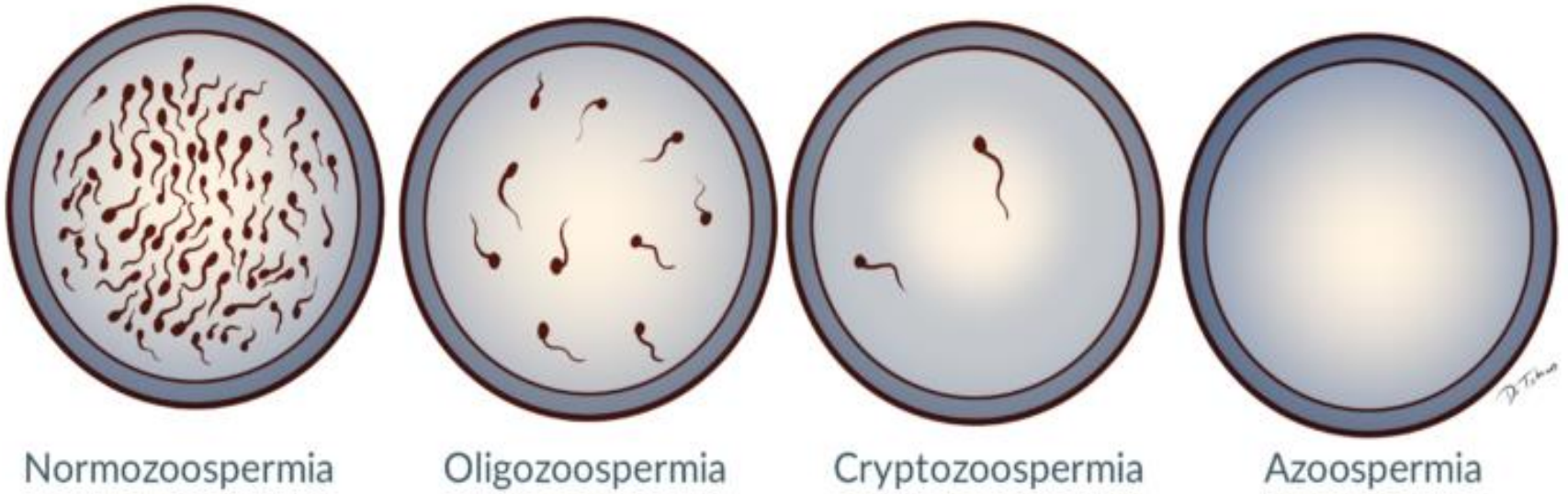
Utilità in sottogruppi

→ Indication “creep”




Cimadomo et al., Eur J Obstet Gynecol Reprod Biol. 2025 Sep

# ICSI e fattore maschile



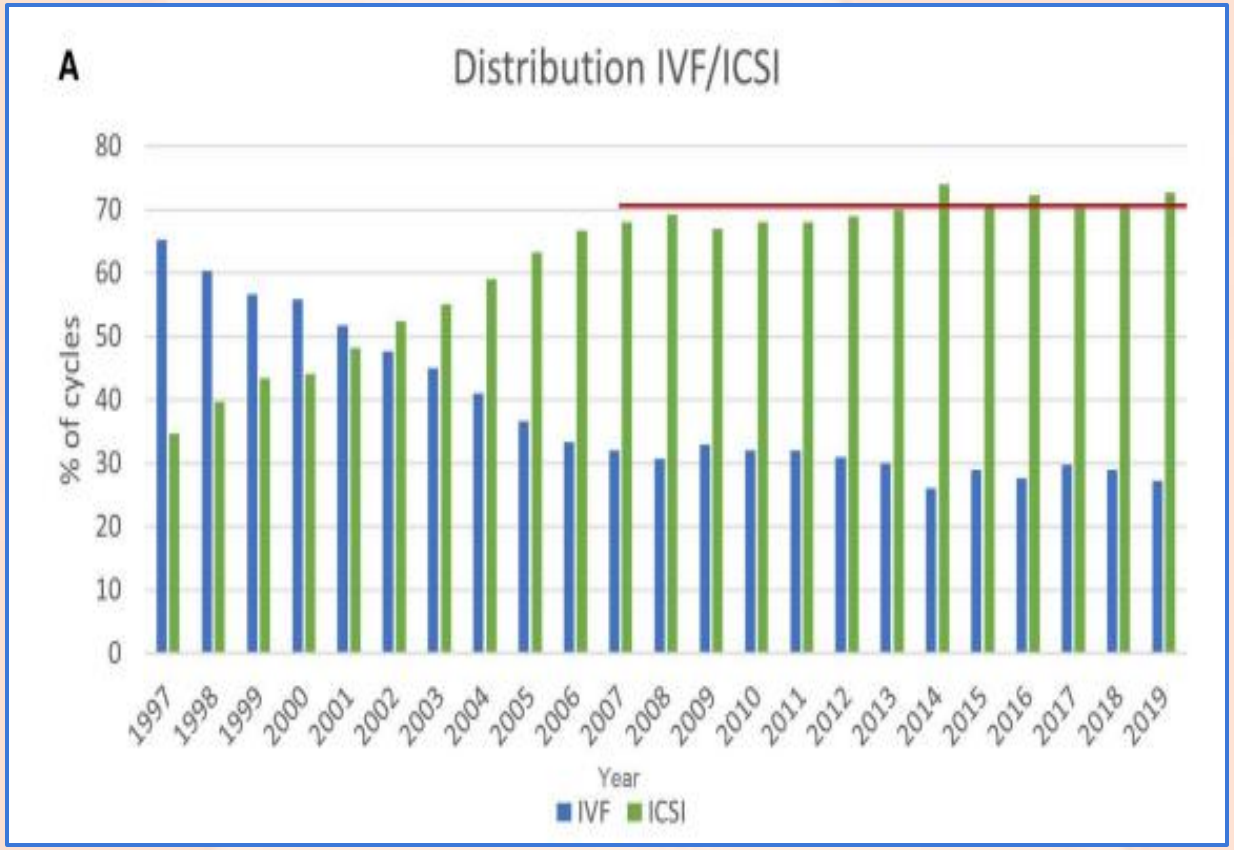



*vantaggio*

# “Indication Creep” → Europa

Over the years, the use of ICSI has extended beyond its original indication for cases of male factor infertility.

Approximately **three-fourths** of all IVF cycles in Europe utilized **ICSI**, including a majority of cases without male factor indications.



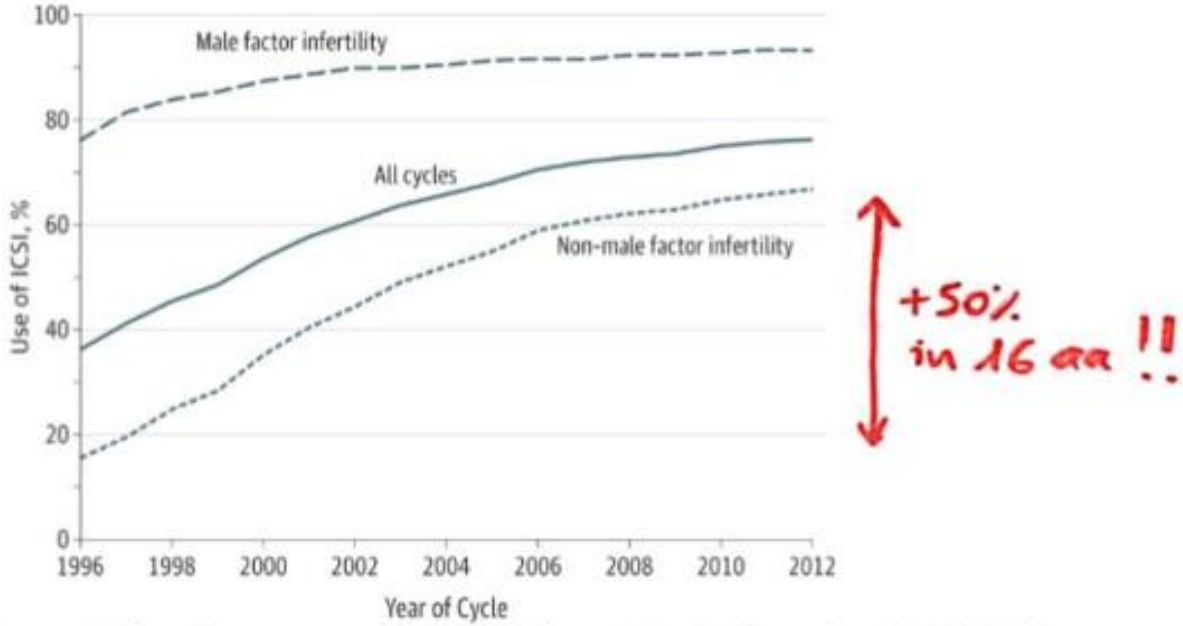

J Smeenk, et al, **ART in Europe, 2019: results generated from European registries by ESHRE**, *Human Reproduction*, 2023

# “Indication Creep” → U.S.A.

*JAMA*. 2015 January 20; 313(3): 255–263. doi:10.1001/jama.2014.17985.

## Trends in Use of and Reproductive Outcomes Associated With Intracytoplasmic Sperm Injection

**Sheree L. Boulet Dr, PH, MPH, Akanksha Mehta, MD, Dmitry M. Kissin, MD, MPH, Lee Warner, PhD, Jennifer F. Kawwass, MD**, and **Denise J. Jamieson, MD, MPH**




Male factor infertility was reported for 499 135 cycles (35.8%)

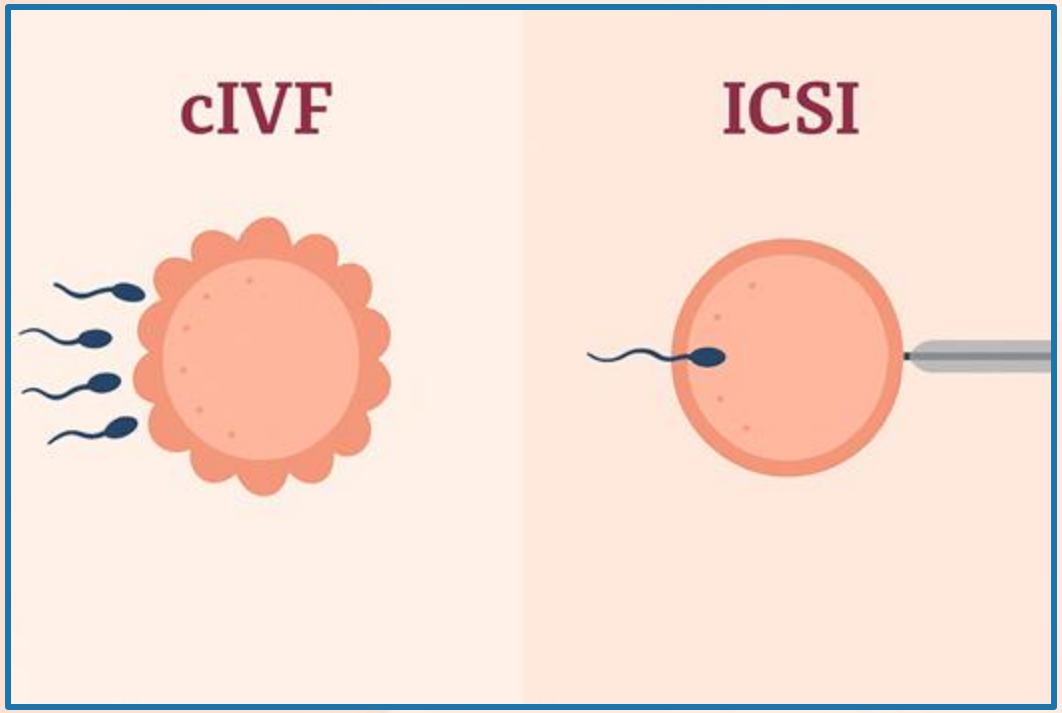
ESHRE European IVF Monitoring Consortium, 2023
ICSI in about 70% of all IVF cycles in Europe

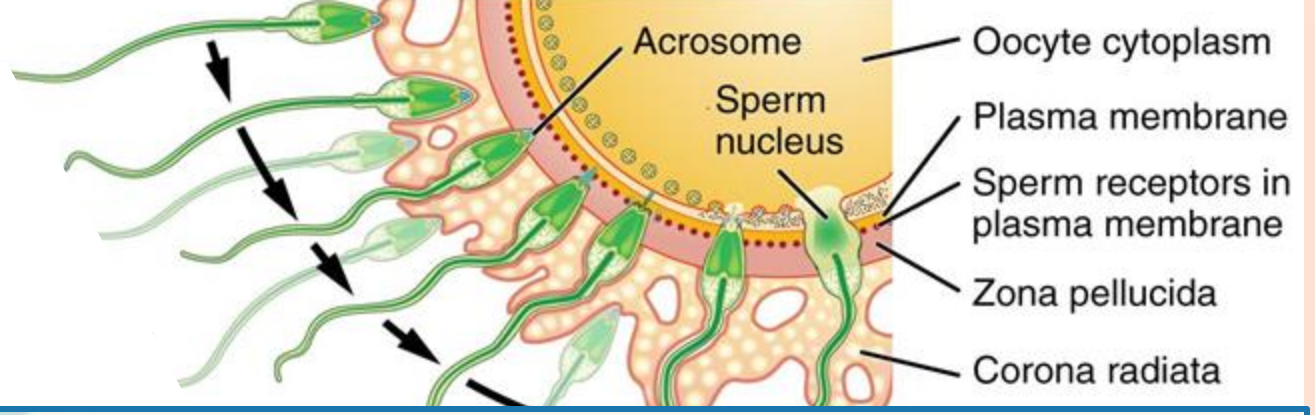
# Why this overuse?

- Health insurance coverage
- Patients preferences
- Difficult communications
- PGT-A
- Clinical practise patterns
- Incomplete awareness of outcomes

Courtesy Paola Viganò

# E’ un vantaggio effettuare ICSI anche in assenza di un fattore maschile severo?






1. Sperm-Egg Recognition.
2. Acrosome Reaction.
3. Fusion.
4. Syngamy.
5. Zygote Formation.
6. Cleavage.

**Standard IVF** **ICSI**

**Pros**
**Cons**

# Intracytoplasmic sperm injection versus conventional in-vitro fertilisation in couples with infertility in whom the male partner has normal total sperm count and motility: an open-label, randomised controlled trial

*Vinh Q Dang, Lan N Vuong, Tam M Luu, Toan D Pham, Tuong M Ho, Anh N Ha, Binh T Truong, Anh K Phan, Dung P Nguyen, Thanh N Pham, Quan T Pham, Rui Wang, Robert J Norman, Ben W Mol*

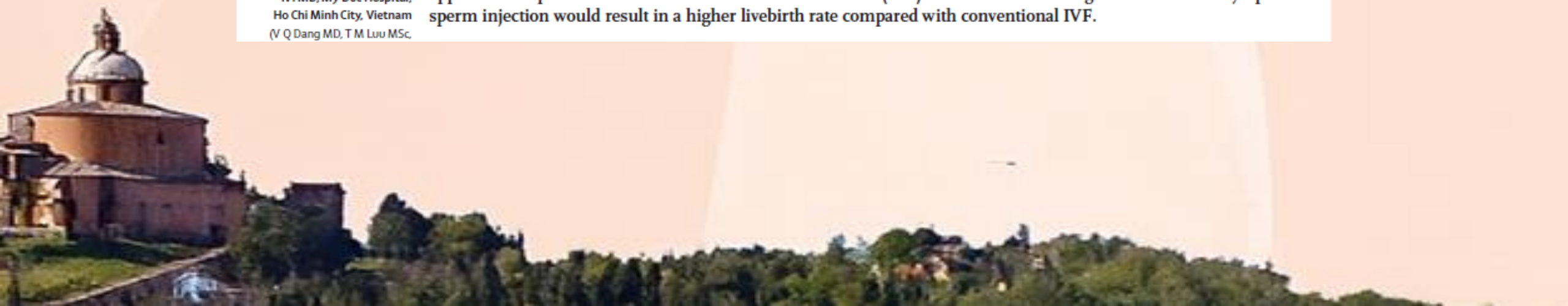
*Lancet* 2021; 397: 1554–63

See Comment page 1521

IVFMD, My Duc Hospital, Ho Chi Minh City, Vietnam (V Q Dang MD, T M Luu MSc,

## Summary

**Background** The use of intracytoplasmic sperm injection has increased substantially worldwide, primarily in couples with non-male factor infertility. However, there is a paucity of evidence from randomised trials supporting this approach compared with conventional in-vitro fertilisation (IVF). We aimed to investigate whether intracytoplasmic sperm injection would result in a higher livebirth rate compared with conventional IVF.



| | Intracytoplasmic sperm injection (n=532) | Conventional IVF (n=532) | Absolute difference (95% CI) | Risk ratio (95% CI)* | p value |
|---|---|---|---|---|---|
| **Fertility outcomes** | | | | | |
| Livebirths† | 184 (35%) | 166 (31%) | 3·4% (−2·4 to 9·2) | 1·11 (0·93 to 1·32) | 0·27 |
| Fertilisation per oocyte inseminated or injected‡ | 75·0% (56·9–88·9) | 66·7% (50·0–83·3) | 5·6% (2·2 to 8·6) | .. | <0·0001 |
| Fertilisation per oocyte retrieved | 58·3% (40·0–72·7) | 55·6% (38·8–70·0) | 2·9% (0·0 to 5·7) | .. | 0·048 |
| Abnormal fertilisation per oocyte inseminated or injected‡ | 1·3% (6·2) | 7·4% (12·4) | −6·1% (−7·6 to −5·1) | .. | <0·0001 |
| Abnormal fertilisation per oocyte retrieved | 1·1% (5·7) | 6·3% (10·5) | −5·2% (−6·5 to −4·4) | .. | <0·0001 |
| Total fertilisation failure§ | 29 (5%) | 34 (6%) | −0·9% (−4·0 to 2·1) | 0·85 (0·53 to 1·38) | 0·60 |
| Couples without an embryo for transfer¶‖ | 8 (2%) | 21 (4%) | −2·4% (−4·6 to −0·3) | 0·38 (0·17 to 0·85) | 0·024 |
| Number of day 3 embryos | 5 (3–8) | 5 (2–8) | 0 (0 to 1) | .. | 0·19 |

# Intracytoplasmic sperm injection versus conventional in-vitro fertilisation for couples with infertility with non-severe male factor: a multicentre, open-label, randomised controlled trial

*Yuanyuan Wang*, Rong Li*, Rui Yang*, Danni Zheng*, Lin Zeng*, Ying Lian, Yimin Zhu, Junli Zhao, Xiaoyan Liang, Wen Li, Jianqiao Liu, Li Tang, Yunxia Cao, Guimin Hao, Huichun Wang, Hua Zhang, Rui Wang, Ben W Mol, Hefeng Huang†, Jie Qiao†*

*Lancet* 2024; 403: 924–34

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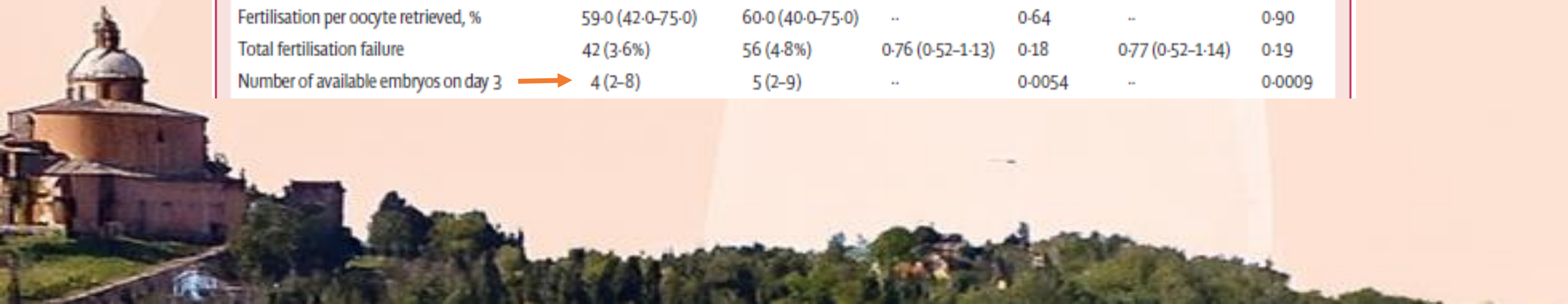
https://doi.org/10.1016/S0140-6736(23)02416-9

## Summary

**Background** Introduced in 1992, intracytoplasmic sperm injection (ICSI) was initially indicated for severe male infertility; however, its use has since been expanded to non-severe male infertility. We aimed to compare the efficacy and safety of ICSI versus conventional in-vitro fertilisation (IVF) in couples with infertility with non-severe male factor.

| | ICSI group (n=1154) | Conventional IVF group (n=1175) | Unadjusted RR* (95% CI) | Unadjusted p value | Adjusted RR† (95% CI) | Adjusted p value |
|---|---|---|---|---|---|---|
| **Primary outcome** | | | | | | |
| Number of live births | 390 (33·8%) | 430 (36·6%) | 0·92 (0·83–1·03) | 0·16 | 0·92 (0·83–1·03) | 0·16 |
| **Fertility outcomes** | | | | | | |
| Implantation rate‡ | 564/1642 (34·3%) | 620/1644 (37·7%) | 0·91 (0·83–1·00) | 0·045 | .. | .. |
| Clinical pregnancy | 463 (40·1%) | 498 (42·4%) | 0·95 (0·86–1·04) | 0·27 | 0·95 (0·86–1·04) | 0·28 |
| Multiple pregnancy | 103 (8·9%) | 124 (10·6%) | 0·85 (0·66–1·08) | 0·21 | 0·85 (0·66–1·08)§ | 0·21 |
| Twin pregnancy | 99 (8·6%) | 121 (10·3%) | 0·83 (0·65–1·07) | 0·16 | 0·84 (0·65–1·07)§ | 0·16 |
| Triplet pregnancy | 4 (0·3%) | 3 (0·3%) | 1·36 (0·30–6·05) | 0·72 | .. | .. |
| Ongoing pregnancy | 402 (34·8%) | 442 (37·6%) | 0·93 (0·83–1·03) | 0·16 | 0·93 (0·83–1·03) | 0·18 |
| **Embryological outcomes** | | | | | | |
| Number of zygotes with two pronuclei per female partner | 6 (3–10) | 6 (3–10) | .. | 0·14 | .. | 0·12 |
| Fertilisation per oocyte retrieved, % | 59·0 (42·0–75·0) | 60·0 (40·0–75·0) | .. | 0·64 | .. | 0·90 |
| Total fertilisation failure | 42 (3·6%) | 56 (4·8%) | 0·76 (0·52–1·13) | 0·18 | 0·77 (0·52–1·14) | 0·19 |
| Number of available embryos on day 3 | 4 (2–8) | 5 (2–9) | .. | 0·0054 | .. | 0·0009 |



# Evidenze da studi randomizzati

Non significativi vantaggi con ICSI rispetto a cIVF in assenza di fattore maschile severo.

Ma…

con ~1700 pazienti per braccio si ha potenza 80% per rilevare una differenza minima di circa 5 punti percentuali tra i due gruppi. (es. da 50% a ~55%)

non sempre la popolazione in studio rappresenta il "caso medio"

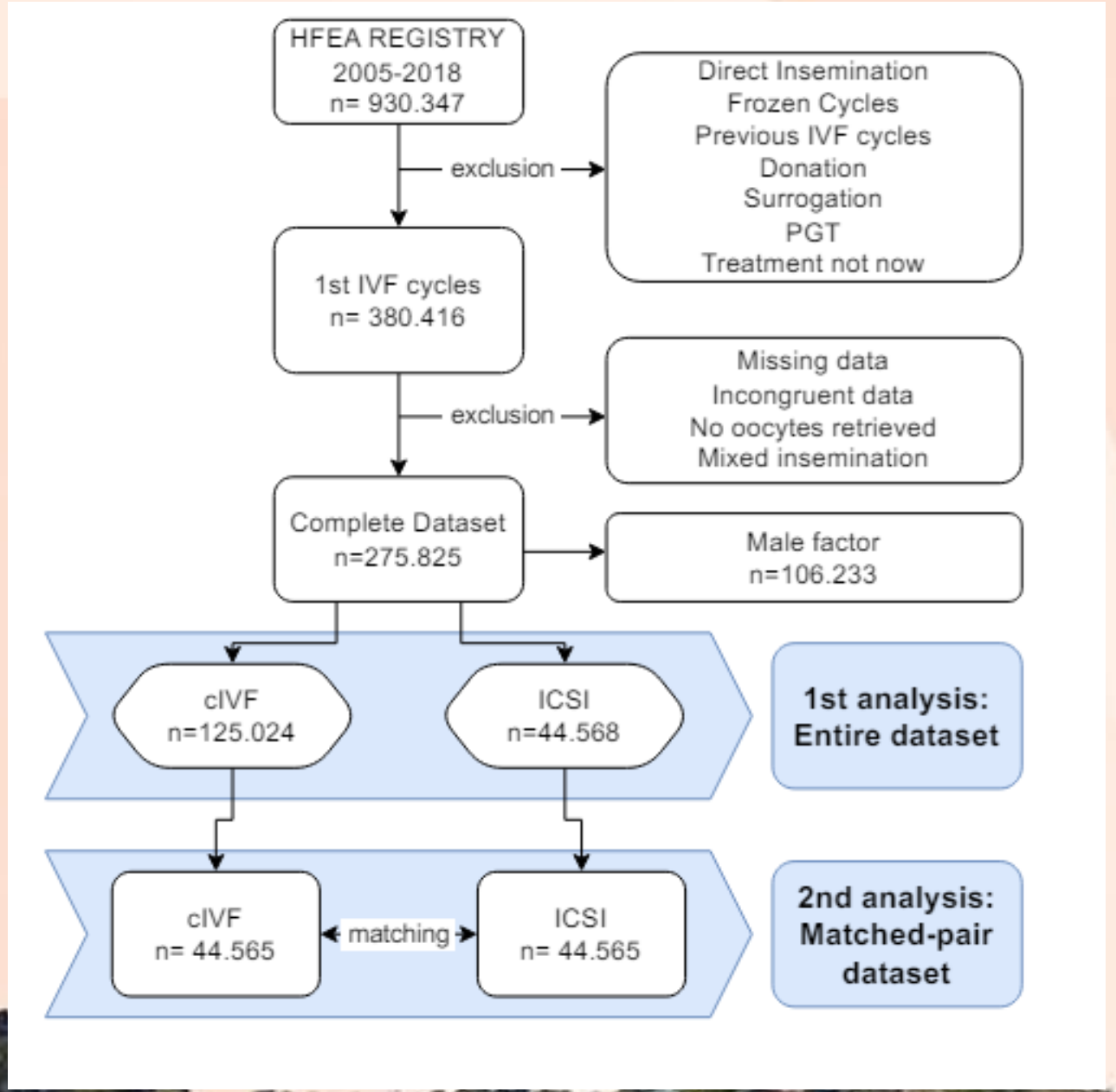
Paffoni et al. Journal of Translational Medicine (2024) 22:687
https://doi.org/10.1186/s12967-024-05515-x

Journal of
Translational Medicine

RESEARCH Open Access

# Intracytoplasmic sperm injection versus conventional in vitro insemination in couples with non-male infertility factor in the 'real-world' setting: analysis of the HFEA registry

Alessio Paffoni[1], Amerigo Vitagliano[2], Laura Corti[1], Edgardo Somigliana[3,4] and Paola Viganò[5*]


HFEA REGISTRY
2005-2018
n= 930.347
exclusion
Direct Insemination
Frozen Cycles
Previous IVF cycles
Donation
Surrogation
PGT
Treatment not now
1st IVF cycles
n= 380.416
exclusion
Missing data
Incongruent data
No oocytes retrieved
Mixed insemination
Complete Dataset
n=275.825
Male factor
n=106.233
cIVF
n=125.024
ICSI
n=44.568
1st analysis:
Entire dataset
cIVF
n= 44.565
matching
ICSI
n= 44.565
2nd analysis:
Matched-pair
dataset

# ICSI vs cIVF

## Unexplained factor

| | ICSI vs cIVF | Entire dataset | Matched-pair dataset |
|---|---|---|---|
| ≈ | **Live birth/cycle** | | |
| | Crude OR | 1,00 (0,97-1,03) | 1,06 (1,02-1,10) |
| | Adjusted OR* | 0,98 (0,95-1,01) | 0,97 (0,93-1,01) |
| ↓ | **Cycle cancellation** | | |
| | Crude OR | 0,60 (0,55-0,64) | 0,60 (0,56-0,64) |
| | Adjusted OR* | 0,72 (0,68-0,76) | 0,64 (0,60-0,68) |
| ↓ | **Implantation** | | |
| | Crude OR | 0,97 (0,95-1,00) | 1,03 (1,00-1,06) |
| | Adjusted OR** | 0,93 (0,91-0,96) | 0,93 (0,90-0,96) |
| ↑ | **Miscarriage** | | |
| | Crude OR | 1,05 (0,98-1,13) | 1,03 (0,95-1,12) |
| | Adjusted OR** | 1,08 (1,01-1,16) | 1,09 (1,00-1,19) |
| ↓ | **Male sex in newborns (in single pregnancies)** | | |
| | Crude OR | 0,86 (0,81-0,92) | 0,88 (0,82-0,95) |
| | Adjusted OR** | 0,87 (0,81-0,92) | 0,88 (0,81-0,95) |

*Adjustment: PCA1, type of female factor, year of treatment

**Adjustment PCA1, PCA2, type of female factor, year of treatment

eshre

# ICSI vs cIVF

## Female factor

| ICSI vs cIVF | Entire dataset | Matched-pair dataset |
|---|---|---|
| **Live birth/cycle** | | |
| Crude OR | 0,96 (0,92-1,00) | 1,01 (0,96-1,07) |
| Adjusted OR* | 0,95 (0,91-0,99) | 0,91 (0,86-0,96) |
| **Cycle cancellation** | | |
| Crude OR | 0,77 (0,70-0,85) | 0,63 (0,57-0,71) |
| Adjusted OR* | 0,72 (0,65-0,79) | 0,66 (0,59-0,74) |
| **Implantation** | | |
| Crude OR | 0,96 (0,92-0,99) | 1,04 (1,00-1,10) |
| Adjusted OR** | 0,92 (0,89-0,96) | 0,92 (0,88-0,97) |
| **Miscarriage** | | |
| Crude OR | 1,13 (1,02-1,24) | 1,19 (1,05-1,35) |
| Adjusted OR** | 1,12 (1,01-1,23) | 1,24 (1,09-1,41) |
| **Male sex in newborns** (in single pregnancies) | | |
| Crude OR | 0,84 (0,77-0,91) | 0,86 (0,77-0,96) |
| Adjusted OR** | 0,83 (0,77-0,91) | 0,86 (0,77-0,96) |

*Adjustment: PCA1, type of female factor, year of treatment

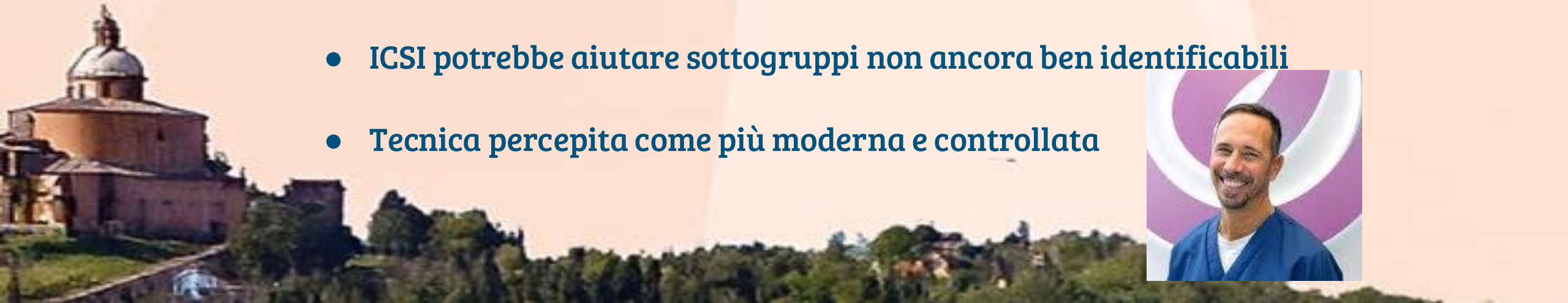
**Adjustment PCA1, PCA2, type of female factor, year of treatment

# ICSI in cerca di equilibrio

# ICSI come Add-on
# Le due interpretazioni opposte

**Posizione A – "Non migliora, ma nemmeno peggiora. Quindi perché non farla?"**

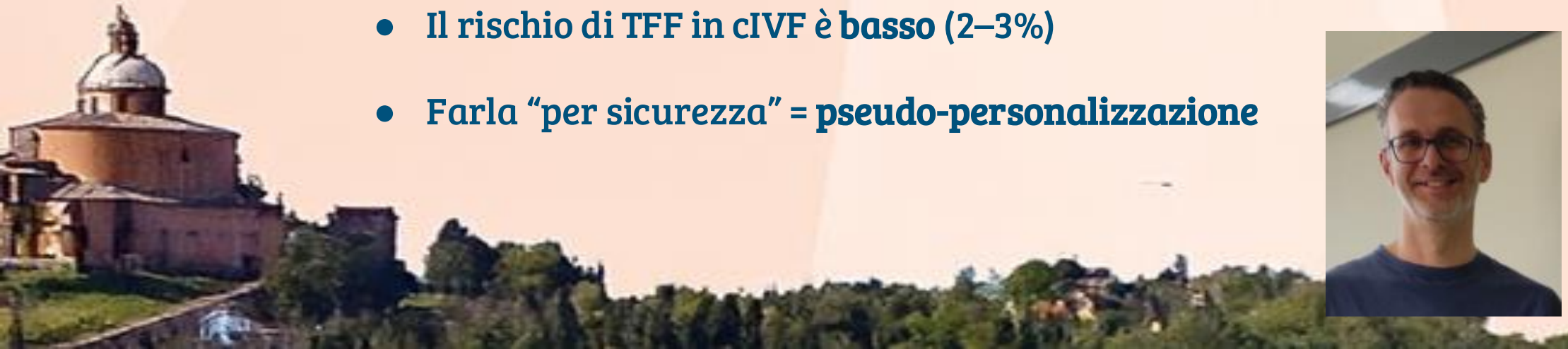
- cIVF e ICSI mostrano outcome simili → nessuna evidenza di danno
- "Meglio stare sicuri": evita il rischio psicologico del Total Fertilization Failure e rende il laboratorio più "standardizzato"
- ICSI potrebbe aiutare sottogruppi non ancora ben identificabili
- Tecnica percepita come più moderna e controllata



# ICSI come Add-on — Le due interpretazioni opposte

**Posizione B – ““Se non dà vantaggi, è un add-on. E gli add-on inutili vanno evitati.”**

- Nessun vantaggio in molte indicazioni non maschili
- Non è neutra: Aumenta manipolazione, tempo tecnico e costi
- Sovrautilizzo → perdita della stretta logica EBM
- Il rischio di TFF in cIVF è **basso** (2–3%)
- Farla “per sicurezza” = **pseudo-personalizzazione**



# La ICSI è utile in caso di specifiche indicazioni, non maschili?

| Indication | Main Findings |
|---|---|
| Advanced maternal age | Most available data fail to demonstrate an advantage of ICSI over c-IVF in terms of fertilization rate, embryo development rate, pregnancy and live birth rates according to the insemination technique. |
| Decreased ovarian reserve | Fertilization rate, fertilization failure, implantation rate, clinical pregnancy rate and live birth rate are comparable after c-IVF and ICSI. |
| Endometriosis | A higher fertilization rate is reported using ICSI, without a significant advantage in terms of implantation rate, pregnancy rate, chemical pregnancy, clinical abortion and ongoing pregnancy rate compared to c-IVF. |
| Autoimmunity | Lower fertilization, clinical pregnancy and live birth rates are documented in partners of antisperm antibodies positive men treated with c-IVF. ICSI can overcome these issues. Superiority of ICSI over c-IVF in couples with thyroid autoimmunity has not been documented. |
| Preimplantation genetic testing | Comparable percentages of embryos with a complete diagnosis and comparable percentages of unaffected/transferable embryos are obtained with c-IVF and ICSI in cycles with genetic testing for aneuploidy. No significant differences in contamination rates of the washing medium samples after c-IVF or ICSI are reported. |
| Single oocyte retrievals | Fertilization, implantation and live birth rates per oocyte retrieval are comparable using c-IVF or ICSI. |

Balli M. et al., J Clin Med. 2022

# L’approccio personalizzato integra

- → evidenze
- → expertise clinica
- → rischio individuale
- → valori della coppia

# Zona a bassa personalizzazione: sicurezza, riproducibilità nel laboratorio

*La biologia pretende stabilità*

Temperatura, pH, gas

Mezzi di coltura

Workflows e SOP

Strumentazione e parametri fissi

Valutazione morfologica standardizzata

# Zona di personalizzazione moderata: decisioni tecniche nel laboratorio

*Qui l'esperienza del laboratorio fa la differenza*

Scelta tra cIVF e ICSI

Percentuale di ovociti da allocare allo split

Giorno del transfer (D3 vs D5)

Freeze-all vs transfer fresco

Timing del warming

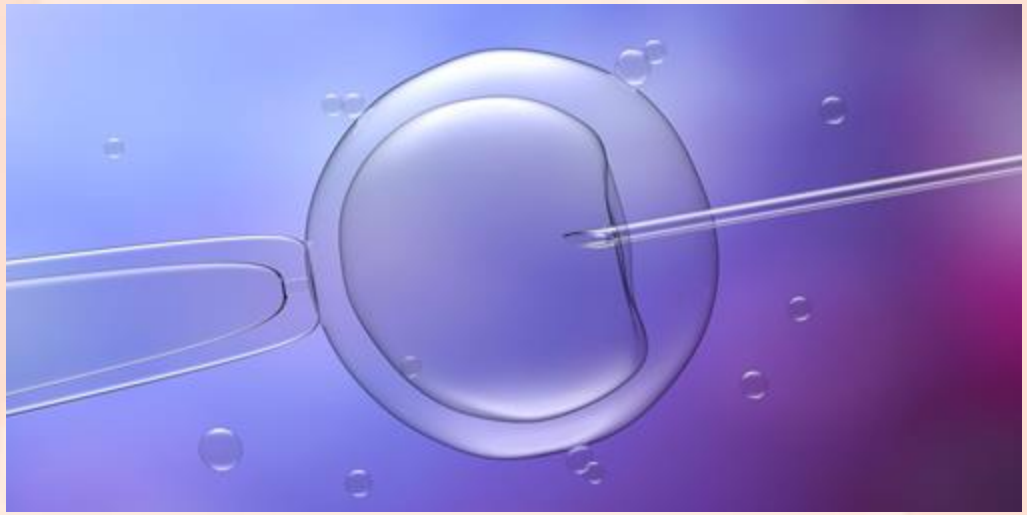
Uso/necessità reale del time-lapse

# Coltura a blastocisti

- Pro: migliore selezione
- Contro: rischio per coppie con pochi ovociti

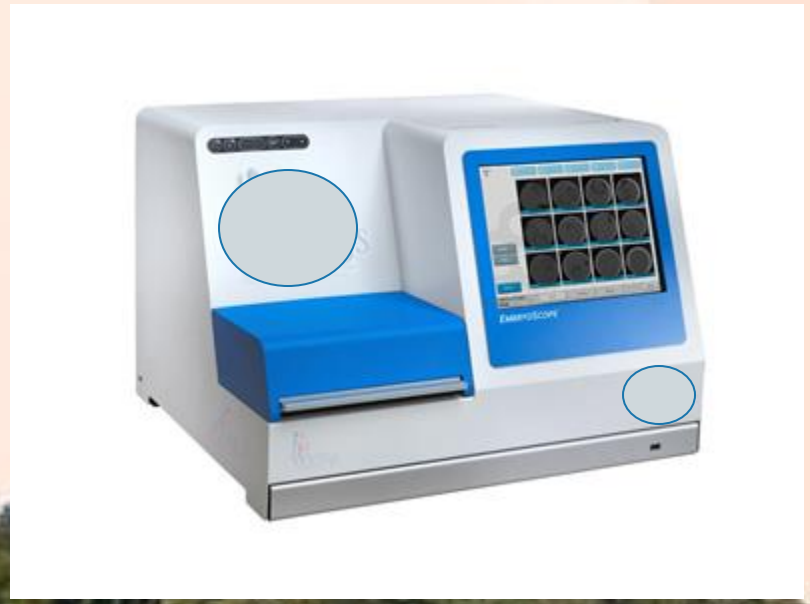
# IMSI/PICSI

- Razionale teorico
- Benefici solo in sottogruppi mirati



# Time Lapse

- Evidenza di aumento della LBR?
- Livello di certezza (molto basso/basso).
- La personalizzazione? → utile per fini specifici (es. logistica, monitoraggio).



# Conclusioni: Miti, Leggende o Realtà?

1. **MITO**: credere a ciò che sembra logico ma non è dimostrato. “Con la ICSI aumentano i tassi di gravidanza anche senza fattore maschile.”

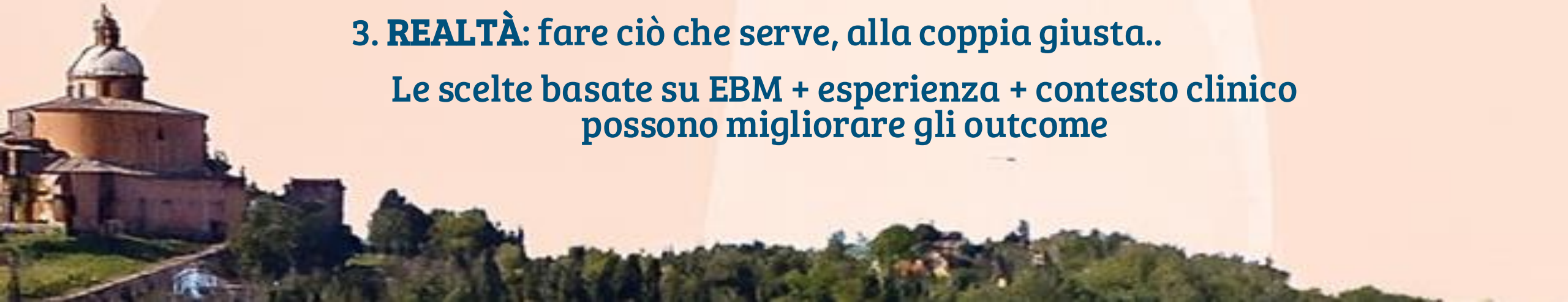
Sembra logico, è rassicurante, ma non è supportato da evidenze.

2. **LEGGENDA e SUPERSTIZIONE**: credere a ciò che potrebbe essere vero. “Trasforma la tecnologia in un talismano contro la paura dell’insuccesso.”

Fare di più per sentirsi più sicuri.

3. **REALTÀ**: fare ciò che serve, alla coppia giusta..

Le scelte basate su EBM + esperienza + contesto clinico possono migliorare gli outcome



# Grazie!

Add-on